

THE PSYCHOSOCIAL FUNCTIONING OF PEDIATRIC CANCER SURVIVORS: THE ROLE OF
NEUROCOGNITIVE ABILITIES

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Dissertation Prepared for the Degree of
DOCTOR OF PHILOSOPHY

UNIVERSITY OF NORTH TEXAS

August 2007

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Begyn, Elizabeth, The psychosocial functioning in pediatric cancer survivors: The role of neurocognitive abilities. Doctor of Philosophy (Psychology), August 2007, 99 pp., references, 172 titles.

With the increase in survival for children with cancer, part of the focus of current research is aimed towards evaluating how these children are adapting psychosocially. Neurocognitive deficits have been well established. However, there are multiple facets encompassing quality of life, including general mental health, lifestyles and health behaviors, and academic and cognitive functioning. The relationship between neurocognitive and psychosocial functioning has yet to be thoroughly evaluated. The purpose of this study was to investigate the relationship between neurocognitive and psychosocial functioning in survivors of brain tumors and acute lymphoblastic leukemia.

Data was collected from existing archival database comprised of patients of the at Cook Children's Medical Center in Texas. The sample consisted of 177 patients between the ages of 3 and 12 who were at least two years post-diagnosis. Measures used included the NEPSY and the Behavioral Assessment for Children. Statistical analyses included a several one-way analysis of variances, an independent samples t-test, a univariate analysis of variance, a hierarchical multiple regression, and odds ratio analyses.

Results indicated survivors treated with neurosurgery alone appear to be less at risk for developing behavior problems than other treatment modalities. Also, brain tumor survivors demonstrate more problematic behaviors than survivors of acute lymphoblastic leukemia. Visuospatial functioning, diagnosis, and type of treatment were

found to be predictive variables of behavior problems. Attention, and perhaps language, deficits may predispose children to more problems in their behavior.

It is concluded that there are other factors affecting behavior in this population that were not accounted for in this analysis. It is recommended for future studies to research the individual clinical scales of the Behavior Assessment System for Children, obtain information from multiple informants, study this relationship longitudinally, and research additional factors that may be influencing the relationship between neurocognitive and psychosocial functioning. This provides evidence of risk factors that should be monitored as the child returns home and to school.

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CHAPTER I

INTRODUCTION

Pediatric cancer is the second leading cause of death in children under the age of 15 in the United States, with 9,100 new cases diagnosed each year. Of these children, half are diagnosed with leukemia or some form of malignant brain tumor (Altman & Sarg, 2000). With advances in hematological and oncological treatment, the current five- year survival rate is 77%, a 45% increase from 1960 (American Cancer Society, 2003). In 2000, 1 in 900 people in the United States between the ages of 15 and 44 were survivors of childhood cancer (Bleyer, 1990). Improvements in survival can be attributed to the introduction of new and improved therapies, namely chemotherapy, bone marrow transplants (BMT) and radiation therapy; centralization of care; and improved supportive care, including the introduction of antiemetic drugs and central venous catheters (Eiser, 2004).

Childhood Cancer Diagnoses

Leukemia

Leukemia, simply defined, is “a class of hematological malignancies in which immortal clones of immature blood cells multiply at the expense of normal blood cells” (Venes, 2001). As a consequence, several side-effects are possible, such as anemia, hemorrhage, or eventual death. Most leukemias cause white blood cells to reproduce abnormally, possibly infiltrating vital organs and glands, causing them to enlarge and malfunction (Altman & Sarg, 2000). Leukemia accounts for one third of all cancer cases in children under the age of 15, thus making it the most common type of pediatric

cancer (American Cancer Society, 2003). Despite the 61% decline in mortality rates over the past three decades, leukemia is still the leading cause of death in children under the age of 15 (American Cancer Society, 2003). However, the long-term survival rate for leukemia ranges between 70 to 80%, depending on the type of leukemia (Margolin & Poplack, 1997).

Each year, nearly 3,700 children in the United States are diagnosed with leukemia, 2,800 of them diagnosed with acute lymphoblastic leukemia (ALL; American Cancer Society, 2003). ALL is the product of the multiplication of mutated B- or T-cell lymphoid cells in the blood, bone marrow, and body tissues (Venes, 2001; Margolin, Steuber, & Poplack, 2001). It is the most common childhood cancer, accounting for almost one-third of all childhood cancers (American Cancer Society, 2002). The average age of onset is four years, usually affecting Caucasians and males more often (The University of Texas MD Anderson Cancer Center, 2001). Of children with ALL, approximately 30% will experience a relapse (American Cancer Society, 1997).

Genetic chromosomal abnormalities may contribute to the development of ALL (Margolin et al., 2001). Other proposed etiologies, including exposure to radiation and toxic chemicals, viral infections, and immunodeficiency have been found to have an indirect, if any, contribution to the development of ALL (Margolin et al., 2001).

The most common symptoms of ALL include: anemia, which is present in 80% of patients; fever; bleeding; and bone pain (Margolin et al., 2001). Tools used in diagnosing ALL include light microscopy and cytochemical stains, immunophenotyping, cytogenetic slides, and molecular analysis. The most significant prognostic indicator of

ALL is elevation in leukocyte counts (Margolin et al., 2001). Once diagnosed, children are classified as either standard or high risk. If children are between the ages of one and nine with a white blood cell (WBC) count less than 50,000/ μ L, they fall into the standard risk range, with a cure rate of over 80% (Gaynon, Angiolillo, Franklin, & Reaman, 2003). When the child is older than age ten and has a WBC count over 50,000 / μ L, they are classified as high-risk.

Treatment of ALL may include chemotherapy, radiation therapy, and in higher risk groups or relapse groups, bone marrow transplant (Jabbour, Faderl, & Kantarjian, 2005). The most common form of treatment is chemotherapy, often followed by radiation therapy (Jabbour et al., 2005). Bone marrow relapse occurs in 30% of children with ALL, while central nervous system (CNS) relapse occurs in 5-10% of cases (American Cancer Society, 1997).

Brain Tumors

The American Brain Tumor Association (ABTA) defines brain tumors as "abnormal growths in the brain resulting from cells reproducing in an uncontrolled manner" (American Brain Tumor Association, 2005). Brain tumors represent the second most common form of pediatric cancer, secondary to leukemia, affecting 3.45 per 100,000 children in children younger than age 15 (Tomita, 2000). Each year, 2,200 brain tumors are diagnosed in children and adolescents in the United States (Bleyer, 1999). The prevalence of brain tumors in children is between 2.2 and 2.5 per 100,000, accounting for 17% of pediatric cancer cases (Spreen, Risser, & Edgell, 1995). Brain tumors are the leading cause of death from childhood cancer. In 1997, brain tumors

accounted for 24% of cancer-related deaths in children younger than 19 (Fuemmeler, Elkin & Mulhern, 2002; National Institute of Neurological Disorders and Stroke, 2001).

Presenting Signs

Although tumors can arise from any brain structure, obstruction of CSF is a common presenting sign, which leads to hydrocephalus, leading to increased intracranial pressure, which causes headaches, vomiting, visual impairment, and lethargy (Ater, Weinberg, Maor, Moore, & Copeland, 2005). Seizures, changes in personality and behavior, such as irritability, symptoms of depression, and suicidal thoughts), and endocrine changes, may also be presenting signs of brain tumors (van Eys, 1991). Furthermore, listlessness, failure to thrive, loss of developmental milestones, focal neurologic deficits/hemiparesis, neuro-endocrine dysfunction, changes in appetite, cranial neuropathies, ataxia, neck pain, and long tract signs (paraparesis or hyperreflexia) are potential presenting symptoms (Ulrich & Pomeroy, 2003).

Certain presenting symptoms may aid in determining the location of the tumor. Localizing symptoms of tumors in the brainstem include diplopia and gaze palsy (Strother, Pollack, Fisher, Hunter, Woo, Pomeroy, et al., 2002). Symptoms of supratentorial tumors, defined as tumors in the cerebrum, basal ganglia, thalamus, hypothalamus, and optic chiasm, may include vision loss (Strother et al., 2002). Signs of infratentorial tumors, located in either the cerebellum or brainstem may include ataxia, gait disturbances, handwriting changes, and speech difficulties, such as dysarthria (Strother et al., 2002).

Most Prevalent Types of Brain Tumors in Pediatric Population

The most common type of brain tumor in children is glial-cell tumors, also known as astrocytomas, accounting for 52% of all CNS malignancies in children (Fuemmeler et al., 2002). Astrocytomas are star-shaped cells arising from connective tissue, found mostly in the cerebrum, and described by their degree of malignancy. Degrees of malignancy include low-grade, mid-grade, and high-grade. Low-grade astrocytomas are usually benign, such as juvenile benign pilocytic astrocytoma, found in the parietal lobe, and treated typically by surgery alone (Armstrong & Mulhern, 1999). Mid-grade astrocytomas include anaplastic astrocytomas. With a five-year survival rate, prognosis is between 73 and 95% (Fuemmeler et al., 2002). High grade astrocytomas, such as glioblastoma multiforme, are the more likely to spread to neighboring healthy tissue and are aggressive (American Brain Tumor Association, 2005). Treatment usually involves neurosurgery in combination with radiation therapy. The 5-year survival rate ranges between 4 and 37% (Fuemmeler et al., 2002).

The second most common type of brain tumor found in children is medulloblastomas. Medulloblastomas are the most common form of primitive neuroepithelial tumors (PNETs) localized in the cerebellum, and may spread to the rest of the brain or spinal cord (Altman & Sarg, 2000). They account for 10-20% of all childhood brain tumors (Ulrich & Pomeroy, 2003; Fuemmeler et al, 2002). Medulloblastomas affect boys four times more frequently than girls and 80% are identified in children before the age of 14 (Armstrong & Mulhern, 1999). Treatment typically involves surgery, followed by one year of chemotherapy and radiation therapy. The five-year survival rate ranges between 40 to 50% (Armstrong & Mulhern, 1999).

Brain stem gliomas are the third most common form of brain tumor found in children (Fuemmeler et al., 2002). These tumors may grow rapidly or slowly, but rarely spread from their original location (Altman & Sarg, 2000). Surgical resection is possible for isolated tumors that arise out of the brain stem, in the medulla, and in the upper portion of the spinal cord. However, brainstem gliomas are not typically treated by surgery because of their remote location and the complex areas they control (Medical College of Central Georgia, 2002). Typically, treatment involves whole-brain radiation therapy. In most cases, survival is only one-year post diagnosis (Fuemmeler et al., 2002).

Finally, ependymal tumors account for 5-10% of all pediatric brain tumors (Ater et al., 2005). These tumors begin in the ependyma, which is a membrane in the brain that stores cerebrospinal fluid (Venes, 2001). Approximately 60% of cases are diagnosed in children before the age of five (Varni, Blount, & Quiggins, 1998). Treatment usually involves surgical resection, followed by radiation therapy. Often, a shunt is required to reduce intracranial pressure in the patient (American Brain Tumor Association, 2005). In 2002, survival rates ranged between 30 and 67% (Fuemmeler et al., 2002).

Late effects

Of supratentorial tumors, including low-grade and high-grade astrocytomas, associated late effects include poor cognitive function, poor manual dexterity, emotional difficulties, seizures, eye-hand coordination problems, hemiplegia, and poorer overall quality of life. In infratentorial tumors, including cerebellar astrocytomas and

ependymoma, late-effects may include ataxia, primary thyroid dysfunction, or ovarian dysfunction (Anderson, Rennie, Ziegler, Neglia, Robinson, & Gurney, 2001). Additional late side-effects may include pain, seizures, and sensory loss (Anderson et al., 2001).

Barr, Simpson, Whitton, Rush, Furlong, and Feeny (1999) found that one-third of 44 children with brain tumors experienced chronic pain. Pediatric brain tumor survivors may also be at risk for visual and hearing impairment. Foreman, Faestel, Pearson, Disabato, Poole, Wilkening, et al. (1999) found that 19% of long-term survivors experienced frequent pain and 15% were deaf, blind, or mute.

Treatments Used in Pediatric Cancer Population

Neurosurgery

Many brain tumors are treated via neurosurgery, which actually places brain structures at further risk for damage (Armstrong, Blumberg, & Toledo, 1999). In truth, neurosurgery is often the primary treatment for brain tumors in children (Tomita, 2000). The more complete the resection, the better the outcome (Strother et al., 2002). The more complete resections improve the efficacy of additional therapies, i.e. chemotherapy and radiotherapy (Ater et al., 2005). Other functions of neurosurgery are to reduce intracranial pressure and for diagnostic purposes (Ater et al., 2005). Prior to surgery, it is safer if increased intracranial pressure can be relieved via external ventricular shunts (Ater et al., 2005). Corticosteroids may also be given prior to surgery to decrease edema (Ater et al., 2005).

Side-effects

Complications of surgery may result from the necessity of the surgeon to remove sections of normal brain tissue to completely remove the tumor (Shenoy, n.d.). Some children may become blind, experience severe coordination problems, ataxia, or speech and language difficulties (Mulhern, 1994). Early side effects may include cosmetic changes, hormone or fluid imbalance, seizures, problems with sight, speech, hearing, movement, strength, learning (Shenoy, n.d.). Mortality resulting from neurosurgery is around 1% for experienced surgeons (Albright, 1993).

Chemotherapy

Chemotherapy drugs are used in the pediatric cancer population for several reasons: in multi-drug regimens to overcome drug resistance and increase chances for complete cancer remission (combination chemotherapy) and after radiation therapy and/or surgery to reduce the risk of metastatic recurrence (adjuvant chemotherapy; Adamson, Balis, Berg, & Blaney, 2006).

Method of Action

Many forms of anticancer drugs interrupt the formation or function of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) cells. The goal of chemotherapeutic agents is to damage the DNA of cancer cells, stop cancer cells from replicating by stopping the creation of new DNA strands, or ending cancer cell division and cancer progression (Ophardt, 2003). For example, certain chemotherapeutic agents may interrupt topoisomerases, a stage critical for DNA maintenance, causing strands of DNA to tear (Adamson et al., 2006). In response to the effects of most cancers in disrupting normal cell functioning (namely the cell cycle and programmed cell death),

the mechanism of chemotherapeutic agents is to induce cell death (apoptosis) in cells sensitive to them (Adamson et al., 2006).

Delivery Mechanisms

Intrathecal chemotherapy (ITC) is a technique used to administer chemotherapeutic agents directly into the cerebral spinal fluid (CSF) space, allowing tumor cells to be exposed to higher concentrations of the drugs (Tomita, 2000). Intrathecal chemotherapy may be administered via frequent spinal taps or via Omayya reservoir, which involves implanting a catheter into the lateral ventricle (Tomita, 2000). This technique is superior to spinal taps because it is less painful for the child and allows for better distribution of the chemotherapeutic agent throughout the CSF (Tomita, 2000). Systemic chemotherapy, on the other hand, is administered into a vein, muscle, or is swallowed as a pill. This mechanism delivers the chemotherapeutic agent throughout the body, making it a useful technique for diseases such as lymphoma (American Cancer Society, 2006).

Types of Chemotherapeutic Drugs

Antimetabolites.

Antimetabolites are chemotherapeutic drugs most effective in interfering with cells that are synthesizing DNA (Adamson et al., 2006). These agents act to increase the amount of the tumor cell population exposed to their drug during DNA replication, making defective DNA or RNA products (Adamson et al., 2006).

Methotrexate, one of the most common antimetabolite agents used in pediatric oncology, is a structural analog to folic acid (Adamson et al., 2006). It is often used for

treatment of ALL, lymphoma, and osteosarcoma. Since cell enzymes mistake methotrexate as folic acid, these cells bind strongly with the drug. This causes the conversion of folic acid to tetrahydrofolic acid, necessary for DNA synthesis, to not occur. Thus, tumor cell division is halted (Ophardt, 2003). Methotrexate doses typically range between 7.7 to 30.0 mg and are administered via oral, muscular, subcutaneous, intrathecal, or intravenous (IV) routes (Adamson et al., 2006). Methotrexate may cause learning difficulties, precipitate seizures, cause permanent damage to the liver and kidneys, and weaken bones (Shenoy, n.d.). Other toxic effects from methotrexate exposure may include hepatic toxicity, mucositis, and osteopathy (Adamson et al., 2006).

Alkylating Agents.

Alkylating agents are chemotherapy agents used to treat cancer because of their ability to interfere with cell metabolism (Venes, 2001). There are three mechanisms in which these agents prevent tumor cells from the miscoding DNA (Ophardt, 2003). One mechanism damages DNA templates via the DNA crosslinks, which are bonds between atoms in DNA, interrupting synthesis or transcription of DNA (Ophardt, 2003). The second mechanism inhibits DNA mutation by causing the mispairing of nucleotides, the structural unit of DNA and RNA. Finally, alkylating agents work by attempting to fragment DNA by attaching alkyl agents to DNA bases (Ophardt, 2003).

Higher doses for alkylating agents are used due to the high drug-response relationship. Side-effects may include, but are not limited to, inhibition of the function of bone marrow (myelosuppression; Venes, 2001), allergic reactions, nausea, and

gastrointestinal toxicity (Adamson et al., 2006). More long-term effects can negatively influence future reproduction via gonad atrophy, renal effects, scarring of the lungs, and kidney damage (Adamson et al., 2006).

The most commonly used of the alkylating agents are the nitrogen mustards and the nitrosoureas. Cyclophosphamide, a type of nitrogen mustard, is one of the most used anticancer drugs in the pediatric population. Typical doses range from 250-1800 mg and are administered via IV. This drug is often used to treat neuroblastomas, leukemia, lymphomas, and sarcomas (Adamson et al., 2006). Of the nitrosoureas, 2-chloroethyl derivatives, carmustine, and lomustine are the most commonly used. Less commonly used groups include ethylenimines, alkylsulfonates, triazenes, and piperazines (Ophardt, 2003).

Antitumor Antibiotics.

Antitumor antibiotics stop tumor cell reproduction by squeezing between the base pairs of the DNA double helix (known as intercalation) and interfering with the shape structure of the DNA strands (Adamson et al., 2006). The drugs from this category used in the pediatric cancer include anthracyclines, mitoxantrone, dactinomycin, and bleomycin.

The anthracyclines are the most widely used of the antitumor antibiotics (Ophardt, 2003). These drugs function by interfering with topoisomerases, preventing DNA tangling by severing and reattaching DNA strands during DNA functions (Adamson et al., 2006). Examples of anthracyclines include doxorubicin, daunomycin, and idarubicin. Doxorubicin is often used to treat solid tumors, while daunomycin and

idarubicin are used to treat leukemias and lymphomas (Adamson et al., 2006; Ophardt, 2003).

Mitroxantrone is used to treat leukemias and lymphomas (Adamson et al., 2006). Functioning similarly to the anthracyclines, mitroxantrone causes breaks in the DNA strands. Mitroxantrone is typically administered daily at 8 to 12 mg doses. Side-effects may include a bluish tint of the fingernails, sclera, and urine, mild nausea, alopecia, and myelosuppression (Adamson et al., 2006).

Although dactinomycin has been in use for 40 years, it has largely been replaced by the anthracyclines for treatment (Adamson et al., 2006). This drug functions as an anticancer drug by binding to the DNA and causing breaks in the DNA strands, blocking elongation of the DNA chain (Adamson et al., 2006; Ophardt, 2003). Dactinomycin is administered via IV at 0.45 mg doses. The bleomycins are used to treat lymphomas and testicular cancers.

Plant products.

Three different plant derivatives used in treatment of childhood cancer, including the vinca alkaloids, derived from the periwinkle plant; the epipodophyllotoxins, derived from mandrake roots; and the taxanes, derived from the *Camptotheca acuminata* tree, are still under investigation for their utility in the pediatric oncology population (Adamson et al., 2006). Vinca alkaloid drugs function by binding to tubulin, which is a major component of microtubules. The development of microtubules is thus interrupted, affecting various cell functions, including mitosis, the movement of such solutes as

neurotransmitters and hormones, and the cell structure itself (Adamson et al., 2006). Types of vinca alkaloids include vincristine, vinblastine, and vinorelbine.

Vincristine is widely used in combination therapy for ALL treatment, as well as being involved in the treatment for neuroblastomas, brain tumors, and lymphomas. Vincristine doses typically range between 1.0 to 2.0 m² and are administered via IV every one to three weeks (Adamson et al., 2006). Side-effects may include peripheral neuropathy, neurotoxicity, cranial motor nerve effects, nausea, inappropriate antidiuretic hormone syndrome, and seizures (Adamson et al., 2006).

Vinblastine is often used to treat lymphomas and testicular cancer. Typically administered in one to three week cycles, doses range between 3.5 to 6.0 mg per m² (Adamson et al., 2006). Vinorelbine is the newest vinca alkaloid drug and has good implications for acute leukemias and chronic myelogenous lymphoma. It is administered via infusion weekly at 30 mg per m² doses for up to six weeks (Adamson et al., 2006).

The epipodophyllotoxins, including etoposide and teniposide, are responsible for DNA strand breaks. This drug classification may be administered to children with leukemia, neuroblastomas, brain tumors, and lymphomas (Adamson et al., 2006). Administration of these drugs is usually over three days, at doses of 60 to 120 mg per m² per day for etoposide and 70 to 80 per m² per day for teniposide. These chemotherapy agents may also be used preoperatively for bone marrow transplants (Adamson et al., 2006).

The taxanes drugs function by interfering with microtubule functioning, eventually leading to cell apoptosis. Paclitaxel and docetaxel, which are used often in

adult cancer treatment regimens, are not necessarily appropriate for pediatric regimens. Camptothecins, including topotecan and irinotecan, alter cell development by causing breaks in the DNA strands. Topotecan may be used to treat neuroblastomas or rhabdomyosarcomas at daily doses of 1.4 to 4.5 mg via IV or oral administration. Irinotecan may be used to treat neuroblastomas, rhabdomyosarcoma, and various CNS tumors (Adamson et al., 2006). However, irinotecan's utility in pediatric treatment is undetermined.

Additional Physical side-effects of Chemotherapy

Drug treatments may result in hair loss, weight gain or loss, fatigue, constipation, low blood counts, and temporary problems with peripheral nervous system functioning (Copeland, Dowell, Fletcher, Sullivan, Jaffe, Cangir, et al., 1988; Margolin & Poplack, 1997). Early side effects at the completion of therapy may include increased susceptibility to infection, low blood counts, nausea, loss of appetite, hair loss, neuropathy, sensitivity to sunburn, and constipation or diarrhea (Shenoy, n.d.).

Radiation Therapy

Radiation therapy may be considered for children with brain tumors after surgical approaches have been ruled out. It is often given to children with CNS tumors, either locally to the tumor site or to the entire brain and spinal cord (Anderson et al., 2001), ranging between 30 gray radiation (Gy) doses to 60 Gy doses. In children with ALL, doses are generally around 18 to 24 Gy (Anderson et al., 2001).

Types of Radiation Therapy

Conventional external beam radiotherapy.

Conventional radiotherapy employs constant dose intensity across the radiation field (Tarbell et al., 2006). This technique exposes everything in the path of the radiation ray (Tomita, 2000). This technique is often performed while the child is outpatient and is delivered five days a week for five to six weeks (Tomita, 2000). The most common disadvantage to conventional radiotherapy is the inclusion of normal brain tissue in exposure to radiation agents. Tumors may reoccur in the irradiated area years later (Tomita, 2000).

Focal Radiotherapy (also known as Conformal Radiation).

Focal radiotherapy aims to direct radiation doses to the tumor, with minimal exposure to surrounding healthy tissue. Thus, focal radiotherapy results in less toxicity and lower long-term side-effects, superior to conventional radiotherapy (Ater et al., 2005). M.D. Anderson uses computed tomography (CT) scans at 3mm slices to obtain the precise location of the child's tumor, outlining the tumor and normal tissue for determination of the gross tumor volume (GTV; Ater et al., 2005). If the tumor cannot be viewed clearly with CT scans, higher sensitivity magnetic resonance imaging (MRI) scans can supplement CT scans. In addition to the GTV, the clinical target volume (CTV) must also be determined, especially for malignant tumors, to estimate the number of tumor cells undetected by CT and MRI scans (Ater et al., 2005). Then, the planning target volume is calculated to account for any possible patient movement and to determine the best placement of the radiation beam to maximize exposure to the tumor and minimize exposure to normal structures (Ater et al., 2005).

Intensity-modulated radiotherapy (IMRT) and three-dimensional radiotherapy (3DRT) are two different focal radiotherapy techniques. In both techniques, children are immobilized, CT scans are used, and the GTV and CTV are calculated to prescribe the correct radiation dose (Ater et al., 2005). In 3DRT, several beams from multiple angles, useful for smaller tumor volumes, target the tumor. With 3DRT, 30% less of normal tissue is affected as compared to conventional radiotherapy (Blaney et al., 2006).

IMRT is indicated for more irregularly shaped tumors and tumors near critical structures. In IMRT, the computer assigns different radiation beams specific doses and intensities, thus making the beams heterogeneous (Ater et al, 2005). The tumor is subdivided into units, with each unit possibly being targeted by radiation beams individually, increasing the amount of the radiation dose hitting its target (The Cleveland Clinic, 2003).

Craniospinal radiotherapy (CSRT).

CSRT has been largely used for tumors that have spread through the CSF, such as medulloblastomas, supratentorial PNETs, and aggressive embryonal tumors (Ater et al., 2005). Due to the need for larger radiation doses to target these tumors, this technique has decreased in popularity because of the increased risk for long-term side-effects. To begin, the child is immobilized and has a CT scan taken of their head and spine. Then, the reference points are determined in the brain and spine. An unfortunate side-effect is radiation exposure to the lens of the eyes, possibly causing cataracts (Ater et al., 2005).

Stereotactic radiosurgery.

Stereotactic radiotherapy, either as single-fraction or multiple-fraction radiosurgery, focuses a large number of narrow beams of high dose radiation, via x-ray or gamma-knife, to a focal point (Tarbell, Yock, & Kooy, 2006). Stereotactic frames are used to position patients, imaging their anatomy, and determining the intended direction of the radiation beams (Tarbell et al., 2006). The radiation doses are delivered via continuously rotating beams over several intervals and positions. This technique is often used to reinforce the effects of conventional radiotherapy and for recurrent brain tumors. In single-fraction stereotactic radiosurgery, the patient comes for one day of treatment, in which the stereotactic frame is rigidly fixed to the patient. Thus, they receive one large radiation dose (Tomita, 2000). In multiple-fraction stereotactic radiotherapy, the patient is treated over multiple days and receives a retractable, noninvasive stereotactic frame. This technique is ideal for small brain tumors that are noninvasive and radiographically distinct (Tarbell et al., 2006).

Internal radiation therapy (brachytherapy).

Brachytherapy involves inserting a catheter implant either in a body cavity (intracavity implants) or into tissue in or near the tumor (interstitial implants). Regardless of the technique used, radiation doses are targeted to the cancer tissue, while healthy tissue is relatively spared (Tarbell, et al., 2006). These implants are removed typically in four days after the radiation dose has been delivered to the tumor (Tomita, 2000). The most frequently used radionuclides, which break down by emitting gamma rays (Venes, 2001), include Iridium-192 and iodine-125, which deliver radiation doses continuously while the implant is inserted. This treatment modality has been used

often for pediatric malignancies, including retinoblastoma (Tarbell et al., 2006). Since this technique delivers the radiation dose to a specific location, large and malignant tumors are not good candidates for this radiotherapy method.

Late Reactions to Radiation Therapy

Late-effects may not surface until years post-treatment and are related to the dose and fraction size (Tarbell et al., 2006). Duffner (2004) cited an association between radiation therapy and significant cognitive and growth impairments, particularly in younger children and at higher doses. Children less than three years are most affected (Shenoy, n.d.). Late side-effects of radiation to the brain may affect movement, coordination, intelligence, hormone production, irritation or drying of the eyes, and cataracts. Additional side-effects may include stone formation in the salivary glands, dental problems, food malabsorption, thyroid change (weight gain, cold intolerance), defective heart or lung functioning, decreased functioning of the adrenal gland, and slowed bone growth (Shenoy, n.d.). Also, radiation therapy may increase the risk for the development of a secondary cancer, especially in the previously radiated site (Shenoy, n.d.). Warring and Wallace (2000) reported that radiation could damage both the testes and ovaries.

Bone Marrow Transplant (BMT)

BMT is a treatment option when it's believed other treatments would not realistically result in long-term survival with no reoccurrence of the disease. BMT is also a treatment option for myelosuppression, which results from chemotherapy treatment (Guinan, Krance, & Lehmann, 2002). That is, devastating side-effects of cancer

treatment, either chemotherapy or radiation therapy, include the demise of healthy cells, including hematopoietic stem cells, and the interference with the bone marrow's ability to manufacture blood cells. Hematopoietic stem cells reside in the bone marrow and either divide to become more stem cells, or they mature to become white blood cells (WBCs), red blood cells (RBCs), or platelets, which are essential to healthy immune functioning (National Cancer Institute, 2004). Bone marrow is particularly affected by cancer treatment because its role is to continuously produce new blood cells and facilitate cell division (Kurtzberg & Clements, 2006). Therefore, BMT replaces these stem cells that were destroyed by previous treatment (National Cancer Institute, 2004).

Highly sensitive assays are run to determine histocompatibility between the donor and the recipient. These assays identify the human leukocyte-associated antigens (HLA; Guinan et al., 2002), proteins on cells used to determine compatibility between donor and recipient. The risk for graft- versus- host disease (GVHD) is reduced when the HLA-match is close. That is, identical twins have the same HLA code, therefore the risk of GVHD is minimal. Between 25 and 30% of candidates for BMT have a sibling with the same HLA-matched code. For unrelated donors, the chance of finding a HLA-matched donor jumps to 50% (National Cancer Institute, 2004).

Conditioning Phase

After histocompatibility is determined, the conditioning phase commences. This conditioning regimen serves several purposes, including removing any residual tumor cells and suppressing the host's immune system to reduce the likelihood that donor cells will be rejected. This creates physical space for the donated stem cells to reside

upon transplantation (Guinan et al., 2002). Another function of the conditioning phase is preparation of the stem cells for infusion. This stage includes depleting t-cells from the donor cells in order to reduce the risk for GVHD, removing any malignant cells from the donor stem cells, and reducing the number the red cells (Guinan et al., 2002).

Two weeks prior to transplant, patients are treated with total- body irradiation (TBI) or busulfan (BU), the mainstay of the conditioning phase. However, these treatment regimens vary depending on the disease being treated. Consequently, prior to transplant, these children are exposed to the side-effects of radiation and chemotherapy, with which the effects may endure up to three months post-transplant (Kurtzberg & Clements, 2006).

Types of Transplants

Autologous transplant.

Autologous transplants involve harvesting stem cells from the patient's own bone marrow or peripheral blood (Guinan et al., 2002). Potential contamination of the sample with residual tumor cells is a foremost limitation of autologous transplants. Graft failure may result if the transplanted stem cells are damaged during transplantation or if they fail to kill damaged stem cells existing in the bone marrow (Guinan et al., 2002). While autologous transplants have low overall mortality rate (usually 10% or less), the risk for relapse is quite high, ranging up to 72% (Guinan et al., 2002).

Syngenic transplant.

Syngenic transplants harvest stem cells from an identical twin sibling. Stem cells in identical twins are the same, thus are ideal for transplants. GVHD is not a risk factor

in syngenic transplants. For unknown reasons, patients that have syngenic transplants are at an increased risk for cancer relapse. Therefore, the survival rate is comparable to autologous and allogenic transplants (Efiong-Ekaha, Patel, Kuku, & Ladapo, 2004).

Overall, the likelihood of having identical twins is quite rare (Guinan et al., 2002).

Allogenic transplant.

Allogenic transplants harvest stem cells from donors with an identical HLA code, either from family members, unrelated donors, or from mismatched family members (Guinan et al., 2002). In the United States, children are often donors because they have higher concentrations of stem cells in their bone marrow and peripheral blood (Guinan et al., 2002). Also, people may volunteer to donate, assuming they are between the ages of 18 and 60 and meet the health requirements. Bone marrow is cryopreserved through programs such as the National Marrow Donor Program until needed (Guinan et al., 2002).

In children with ALL with HLA- identical donors, 39% survived disease free, while 30% survived disease free with HLA-mismatched donors (Gluckman, Rocha, & Chastang, 1998). Overall, while disease free survival is decreased with HLA-mismatched donors, these observed differences are diminishing with improvements in the assays used to determine HLA-match (Guinan et al., 2002).

Complications Resulting from BMT

Graft Versus Host Disease (GVHD).

When the transplanted donor stem cells (graft) are recognized by the host cells as foreign and are subsequently attacked, GVHD results. The organs most often

affected include the skin, the liver, and the gastrointestinal system. Therefore, common conditions resulting from GVHD include dermatitis, hepatitis, and enteritis (Guinan et al., 2002). GVHD can be classified as acute, occurring within a few weeks of the transplant, or chronic, with side-effects surfacing a significant amount of time after the transplant (National Cancer Institute, 2004).

Additional side-effects of BMT.

Patients may be more susceptible to infections from prolonged myelosuppression resulting from the BMT procedure. Children may be placed at a heightened risk for secondary malignancies, particularly after autologous transplants (Guinan et al., 2002). Endocrine complications may result, as well as gonad and ovarian failure. Thyroid dysfunction, growth failure, cataracts, renal disturbance, and decreased lacrimation are potential consequences from BMTs (Guinan et al., 2002).

Graft failure is also a possible side- effect. The incidence of graft failure for syngenic transplants is around 1%. For mismatched donors and autologous transplants, the likelihood of graft failure rises to 5 to 10%. Disease relapse is the biggest contributor to graft failure (Guinan et al., 2002).

Additional Treatment Regimens

Corticosteroids may be used in treatment for pediatric brain tumors, ALL, lymphomas, and Hodgkin's disease. They may also be used to treat the side-effects of cancer and cancer treatment. Corticosteroids, including prednisone, dexamethasone, and prednisolone, cause receptor-mediated lympholysis by binding to glucocorticoid receptors (Adamson et al., 2006). Dexamethasone is also used to reduce cerebral

edema around the tumor (Tomita, 2000). Dexamethasone therapy may put children treated for ALL at risk for neurocognitive late effects compared to children treated with prednisone (Waber, Caprentieri, Klar, Silverman, Schwenn, Hurwitz, et al., 2000). Common side-effects include increased appetite, immunosuppression, hypertension, and amenorrhea (Adamson et al., 2006). The uses of steroids for long periods may cause cataracts, weight gain, excess hair growth, steroid dependency, high blood pressure, and diabetes (Shenoy, n.d.; Tomita, 2000). Furthermore, the adrenal glands that normally produce natural steroids in the body may stop functioning properly. Psychiatric side-effects may include hypomania, mood swings, sleep difficulties, anxiety, and personality changes (Brown, 1998).

Asparaginase is an enzyme derived from the bacterium *escherichia coli* or *erwinia cartovora* commonly used for nutritional treatment for ALL and lymphomas (Beers & Berkow, 1999). Asparagine is an amino acid found in the body that is essential for protein synthesis. It functions by depleting asparagine in the blood. Typically, when normal cells detect decreased amounts of asparagine in the body, they are able to produce more. However, cancer cells are unable to produce more, so they die. Asparaginase is administered either through IV or intramuscularly in doses of 6,000 to 25,000 IU per m² three times a week (Blaney, Holcenberg, & Blaney, 2001). Side-effects may include reactions to the bacteria, encephalopathy, clotting of the blood, pancreatitis, or liver damage (Adamson et al., 2006).

Previous Research Regarding Neurocognitive Abilities

Intelligence

Pediatric cancer survivors often exhibit significantly lower performance intelligence quotients (PIQs) and verbal intelligence quotients (VIQs) on the Wechsler scales than their healthy peers (Winqvist, Vainionpaa, Kokkonen, & Lanning, 2001). Brain tumor survivors under the age of 18 exhibited mild cognitive impairment. Survivors demonstrated more difficulties with nonverbal tasks, averaging a mean difference of 7.3 points (Poggi, Liscio, Galbiati, Adduci, Massimino, Gandola, et al., 2005). Children with ALL who underwent radiation therapy with chemotherapy scored 8.7 points lower on full-scale intelligence quotient (FSIQ) than children treated with chemotherapy alone (Langer, Martus, Ottensmeier, Hetzberg, Beck, & Meier, 2002).

Attention and Concentration

The most profound neurocognitive deficits that have been documented in pediatric cancer survivors involve attention and concentration abilities (Mulhern & Butler, 2004). Peckham (1991) conducted a longitudinal study of 18 children treated with 2,400 centi-Gray units (cGY) prophylactic cranial irradiation eight to ten years previously. Therefore, pre and post-treatment intellectual abilities were collected. Visits were made to the child's school, teachers were consulted, parents were interviewed, and children were observed in class and interviewed (when possible). The most frequent problem cited by all sources was with attention and concentration, specifically inner distractibility.

Memory

Memory is another domain of neurocognitive functioning affected by childhood cancer treatment. Memory difficulties have been reported in 50-75% of children with brain tumors (Armstrong et al., 1999). Children with ALL are at increased risk for short-

term memory loss (Dennis, Spiegler, Hoffman, Hendrick, Humphreys, & Becker, 1991). For survivors of ALL, deficits in nonverbal memory and attention were significantly related to deficits in general intelligence, neurocognitive problems, and delays in academic achievement (Moleski, 2000).

Brouwers and Poplack (1990) evaluated verbal memory, nonverbal memory and learning in 23 survivors of ALL treated via cranial irradiation or intrathecal chemotherapy off-treatment for at least four years. Subjects were classified into one of three groups based on their CT scans: normal scans, cerebral atrophy, or intracerebral calcifications. Participants with intracerebral calcifications demonstrated greater information loss and more problems with verbal learning than the other two groups. When evaluating the effect of mean reaction time on learning and memory performances for group differences, analyses demonstrated group differences decreased when adjusting for attentional deficits. Authors concluded that attention abilities are mediating the memory and learning deficits presented in subjects, influencing the encoding of information.

Visual-Motor Integration and Motor Abilities

Visual-motor integration problems and slowing in processing speed have been noted in children with brain tumors (Coniglio & Blackman, 1995; Winqvist et al. 2001). Fine-motor skills and perceptual-motor skills may be negatively affected as a result of CNS chemotherapy, at least in the acute phase of treatment (Moleski, 2000). Kieffer-Renaud, Bulteau, Grill, Kalifa, Viguiet, and Jambaque (2000) found that survivors of

medulloblastomas demonstrate deficits in visuo-constructive skills and manual dexterity, regardless of the strength of radiation dose.

Wright, Halton, Martin, and Barr (1998) studied the motor performance in 36 child survivors of ALL, comparing them to 26 age and gender matched controls. Results found that gross motor tasks that required balance, such as hopping on one foot and jumping, were more problematic for survivors. Hand grip strength, running speed, and agility, were also compromised when compared to controls. Motor impairments were hypothesized to be a side-effect of chemotherapeutic agents, cranial irradiation, and steroids.

Previous Research Regarding Psychosocial Functioning

Several areas of psychosocial functioning have been researched in pediatric cancer survivors, including internalizing behaviors, externalizing behaviors, self-image, social functioning, and academic functioning. Throughout the literature, there are discrepancies in findings.

Internalizing Behaviors

The research is mixed as to the effect of childhood cancer on survivors' mood. More specifically, internalizing behaviors, ranging from depression, anxiety, poor self-image, social withdrawal, and somatic complaints, have been inconsistently reported in children with cancer.

Depression

On one side, researchers state that the child survivor's feelings of control are the factors that ultimately determine their insecurity or confidence. If these children do not

feel a sense of control, they may experience feelings of hopelessness (Last & Grootenhuis, 1998). Chao, Chen, Wang, Wu, and Yeh (2003) administered a depression inventory to 24 pairs of children with cancer and their parents. The participants and their parents completed a psychosocial adjustment questionnaire containing items regarding demographics, psychosocial health characteristics, perception and attribution of the illness, and psychological functioning of the family. Results indicated the children did not rate themselves as having more social, academic difficulties, or depressive symptoms as compared to grade and gender equivalent norms. However, their parents rated them to have more mood disturbances and fewer friends.

Lavigne and Faier-Routman (1992) conducted a meta-analysis of 28 studies, concluding that children with chronic illnesses are at risk for adjustment difficulties. Moreover, survivors are at risk for internalizing behaviors, such as depression or anxiety, opposed to externalizing problems, such as aggression. However, Lavigne and Faier-Routman cautioned that the results from the meta-analysis are dependent on the methodology used in the included studies.

Kunin, Patenaude, and Grier (1995) discovered ten documented or suspected suicide attempts between 1974 and 1991 at the Dana-Farber Cancer Institute. These ten attempts included two successful suicides, four attempts, two deaths from undetermined causes, and two deaths potentially resulting from reckless behavior. Researchers concluded that, in some children, the diagnosis of cancer may, "place an additional, unmanageable demand on already burdened coping resources (p.153)." They discussed several factors that may contribute to increased suicide risk in this

population, including depression and hopelessness, stressful family events, preexisting psychopathology (e.g. substance abuse), loss of control or helplessness, prior suicide history, interpersonal isolation, advanced illness or poor prognosis, and pain management difficulties. They cautioned, however, these numbers may be an underestimation because of the reluctance of health care professionals and families to divulge such information. However, authors concluded the suicide risk for pediatric cancer survivors is similar to those of the general population of children and adolescents.

A higher prevalence of depression has been suspected in children with cancer for two reasons: Depression has been documented as common in children with chronic illnesses and is common in adults with cancer (Eiser, 2004). Bennett (1994) conducted a meta-analysis of 60 studies, concluding that children with physical illnesses are at an increased risk for depressive symptomatology, but do not necessarily meet the criteria for clinical depression. Bennett remarked that parents seemed to endorse more depressive symptoms in their children than children do themselves. Phipps and Sprivastava (1997) suggested that patients rate themselves as having less psychopathology because they tend to adopt a protective coping bias to minimize stress. Children with asthma, recurrent abdominal pain, and sickle cell anemia reported more depression than did children with cancer and diabetes.

Anxiety

Eiser, Hill, and Vance (2000) conducted an analysis of twenty studies in English published since 1990, comparing survivors to matched controls or population norms.

After surveying these studies, they concluded that survivors do not exhibit greater levels of anxiety than others. In fact, many studies have revealed survivors to have a positive outlook toward their past encounter with cancer (Eiser et al., 2000; Zebrack & Chesler, 2002).

Zebrack and Chesler (2002) studied 176 survivors successfully off treatment. Information was gathered from medical charts and a self-report questionnaire to measure quality of life. Survivors reported a healthy ability to cope after their cancer experience, suggesting a resiliency in young survivors against the negative effects of cancer and its treatment.

Hormone levels were checked in children with cancer both on and off treatment on two separate clinic visits (Hockenberry-Eaton, Kemp, & Dilorio, 1994). Physiologically, children had higher epinephrine levels than expected, suggesting they were experiencing a chronic state of stress. Yet, this can be misleading, since their cortisol and norepinephrine levels were still within normal limits.

Self-image

The cancer experience can adversely affect children's perceived sense of attractiveness, as treatment side-effects may include changes in weight, the loss of hair, or skin changes (Eiser, 2004). Onset of cancer during adolescence may cause more distress for the patient compared to early or late onset (Eiser, 2004). Adolescent survivors of cancer may be at increased risk for eating disorders as a result of the side-effects of treatment, including weight gain, interference of normal development, and scarring (Rodin, Daneman, & deGroot, 1993).

Coniglio and Blackman (1995) reported that survivors endorse poorer self-concepts compared to their peers. Also, survivors have been shown to have poorer self-image by reason of changes in their physical appearance (Armstrong et al., 1999; Zebrack & Chesler, 2002). Noll, Gartstein, Vannatta, Correll, Bukowski, and Davies (1999) reported that children with cancer have lower self-confidence in their athletic abilities, perhaps due to reduced energy levels or chronic fatigue. Furthermore, Willoughby, Polatajko, and Wilson (1995) reported that children's motor abilities contribute to their self-esteem, success in therapeutic recreation activities, and overall level of fitness.

In contrast to the studies previously discussed, Maggiolini, Grassi, Adamoli, Corbetta, Charmet, Provantini, et al. (2000) studied self-image in Italian adolescent survivors of ALL. Seventy former patients between the ages of 12 and 20 who had completed therapy at least two years prior were compared to 70 secondary students similar in age and geographic area of residence. Results indicated that adolescent survivors of ALL demonstrate more emotional stability, better self-image and body image, more confidence and socially support, and a general positive attitude compared to their peers.

Zebrack and Chesler (2002) found that childhood cancer survivors endorse a positive quality of life and rate themselves as being able to effectively cope with their illness. Overall, the major predictor of positive emotional outcomes in children with cancer is positive expectations of the future (Last & Grootenhuis, 1998). Elkin, Phipps, Mulhern, and Fairclough (1997) found pediatric cancer survivors report greater

psychological health and well-being, as well as lower psychological distress than would be expected based on healthy controls. While 75% showed some residual cosmetic impairments and 64% had some physical impairments, survivors indicated they were functioning psychologically better than expected.

Externalizing Behaviors

The research on externalizing behaviors in pediatric cancer survivors, such as aggression and substance abuse, is also mixed. Although many of the studies have found that children with brain tumors are not at risk for significant externalizing problems, Rynard, Chambers, Klinck, and Gray (1998) administered the Child Behavior Checklist (CBCL™; Thomas Achenbach, www.aseba.org/products/cbcl6-18.html) and Behavior Assessment System for Children (BASC) Teacher Report Form (TRF™; AGS Publishing, www.agsnet.com) to teenagers on-treatment or recently off-treatment reentering school. While parents rated their survivors to be more aggressive and hyperactive than their teachers, survivors did not demonstrate significant externalizing behavioral problems (Fuemmeler et al., 2002). Mulhern, Carpentieri, Shema, Stone, and Fairclough (1993) revealed several factors relating to elevated behavior problems in children with brain tumors compared to children with other forms of cancer, including: younger maternal age at child's birth, tumor location, and living in a single-parent home.

Mulhern et al. (1993) reported that both the brain tumor and cancer control groups demonstrated similar low levels of social competence and high levels of behavior problems soon after diagnosis. Verrill, Schafer, Vannatta, and Noll (2000) found that young adult cancer survivors report less illegal drug use and experimentation,

concluding that the cancer experience may be protective against the development of externalizing behaviors.

Social Functioning

The literature concerning the social functioning in pediatric cancer survivors is mixed. Mackie, Hill, Kondryn, and McNally (2000) administered the Adolescent to Adult Personality Functioning Assessment (AFBA™; Naughton, Oppenheim, & Hill, 1996) to assess social role performance and interpersonal relationships in long-term survivors of childhood cancer. Researchers found that adult survivors of childhood ALL demonstrated significantly more difficulties in close relationships. Compared to a group of children from pediatric hospitals, 40% of adult survivors of childhood ALL report being teased about their physical appearance and being treated like outcasts (Kazak, Barakat, Meeske, Christakis, Meadows, Casey, et al., 1997).

Butler, Rizzi, & Bandilla (2000) found that over 80% of their sample childhood cancer patients on and off treatment between the ages of 6 and 16 did not meet criteria for significant psychological and adjustment disturbance. Results showed that, as time passed since the first cancer treatment, social incompetence and social skill deficits were more likely to emerge. In the circumstances that psychological difficulties were present, they were more likely to be the result of some situational aspect of the cancer or its treatment. Hill, Kondryn, Mackie, McNally, and Eden (2003) studied 102 adult survivors of childhood ALL or Wilms' tumors and 102 matched controls via standardized interview methods, finding survivors have poorer day-to-day coping abilities and close adult relationships than controls.

Boman and Bodegard (1995) reported that survivors experience impaired social functioning. Spirito, DeLawyer, and Stark (1991) found that their social interactions may suffer due to observable physical differences. Survivors have been rated by their peers to be more socially isolated, withdrawn and have fewer peer friends (Noll, Bukowski, Davies, Koontz, & Kulkarni, 1993; Spirito, Stark, Cobiella, Drigan, Androkites, & Hewitt, 1990).

Hill et al. (2003) found that adult survivors of childhood cancer are more likely to have impaired close relationships, both romantic relationships and friendships. Hays, Landsverk, Sallan, Hewitt, Patenaude, Schoonover, et al. (1992) found a decreased number of marriages or cohabitation relationships among pediatric cancer survivors, suggesting survivors may have difficulties with intimacy and increased interpersonal isolation. While Novakovic, Fears, Wexler, McMillure, Wilson, McCala, et al. (1996) reported that survivors show lower marriage rates and higher divorce rates compared to siblings and population norms, Hays et al. (1992) found no difference in divorce rates compared to population norms.

La Greca (1990) emphasized the difficulty of survivors returning to school, in that they may be dealing with teasing from their peers, as well as harboring feelings that they are different and unattractive. Eiser (2004) posited teasing and social isolation may be even more upsetting than the physical pain associated with the illness and diagnostic procedures.

BMT survivors have also been reported to have more difficulties socially. Vannatta, Zeller, Noll, and Koontz (1998) found that peers rated BMT survivors as

having fewer friends, being more socially isolated, and being less physically attractive. Phipps (2005) found that their social competence, self-esteem, and emotional well-being declined between six months to one year post treatment.

On the other hand, Zebrack and Chesler (2002) found that childhood cancer survivors report a high level of satisfaction in their social relationships. Newby, Brown, Pawletko, Gold, and Whitt (2000) found no significant social skills deficits in 42 children and adolescent cancer survivors participating in a late-effects follow-up clinic. Parents rated poor adjustment in 14% of the sample, while teachers rated poor adjustment in only 7% of the sample. Elkin, Tyc, Hudson, and Crom (1998) found that over half of their sample of long-term survivors participated in organized sports. Of those that did not participate, 64% said they had no difficulties competing with their peers.

van Dongen-Melman and Saunders-Woudstra (1986) reported that any adjustment problems experienced by survivors are transient and mild. School phobias in this population are very rare (Landsky, Lowman, Vats, & Gyulay, 1975). In fact, studies have shown that survivors typically recount their cancer experience as a positive experience (Eiser et al., 2000; Zebrack & Chesler, 2002).

Mediating Variables to Social Functioning

Several studies have addressed contributing factors to social obstacles in survivors. Mulhern et al. (1993) found a relationship between social problems and overt functional status in child and adolescent patients recently diagnosed with cancer, especially in cases when severe debilitation was present. Zebrack and Chesler (2002) found social quality of life to be related to survivors' physical health and their living

situation (alone or with others), suggesting interdependency between physical, social, and psychological variables.

Parental encouragement has been posited to be a contributing factor as well. For female survivors, the lack of encouragement from parents and high levels of maternal involvement were positively associated with poor adult relationships (Hill et al., 2003). However, the authors stated that parental encouragement does not appear to be the major mediator between cancer survivorship and adult functioning.

Also, research suggests that children with brain tumors have an increased probability of developing social competency deficits as compared to their peers with non- CNS tumors and healthy peers (Fuemmeler et al., 2002). Mulhern et al. (1993) found the children with brain tumors in their study demonstrated slightly more problems with social competence, participation in activities, and school performance than the cancer control group.

Finally, another contributing variable is the age of the survivor. Age appears to have an increasing detrimental effect on psychosocial functioning. Adolescents may experience more limitations in social functioning, as they may be forced to rely on their parents and be isolated from their friends because of their condition. Therefore, adolescents with cancer face obstacles in achieving a developmentally appropriate sense of identity and intimacy (Eiser, 2004).

Academic Functioning

As a result of cancer and/or its treatment, more than half of children diagnosed with leukemia or a brain tumor will be at risk for a learning impairment (Armstrong &

Mulhern, 1999). Madan-Swain, Brown, Walco, Cherrick, Ievers, Conte, et al. (1998) found that more than one-third of survivors received special education services part-time, while 7% required full-time services. However, only 8% of their sample met the criteria for a learning disability, while the remaining participants received services based solely on their medical condition. Studies have found that between 26 and 47% of pediatric cancer survivors have repeated a grade (Moore, Glasser, & Albin, 1987; Mulhern, Wasserman, Friedman, & Fairclough, 1989).

Hays, Dolgin, Steele, Patenaude, Hewitt, Ruymann, et al. (1997) conducted phone interviews of 300 cancer survivors ages 20 or older. Researchers discovered that survivors completed fewer years of school, had higher rates of unemployment, lower occupational status, and lower annual incomes compared to matched controls.

Demographic and Treatment Factors Mediating Neurocognitive Functioning and Psychosocial Functioning

There are many mediating effects involved in the effects of cancer and its treatment. The diagnosis and elements of the treatment may modify the psychosocial and neurocognitive presentation of survivors of pediatric cancer. Furthermore, age at diagnosis and gender may influence the effect of cancer and its treatment on psychological and neurocognitive functioning of survivors.

Diagnosis

Diseases that involve the CNS and bone tumors have been associated with more adjustment difficulties (Boman & Bodegard, 2000; Langeveld, Stam, Grootenhuis, & Last, 2002). Brain damage can result from brain tumors, effects of treatment, and

comorbid conditions, such as seizures and hydrocephalus (Mulhern, Hancock, Fairclough, & Kun, 1992). Manne and Miller (1998) found the single most crucial predictor of psychological adjustment in adolescents with cancer was physical impairment.

Children with CNS tumors reported significantly more quality of life difficulties compared to children with ALL and normal population means (Eiser, Greco, Vance, Horne, & Glaser, 2004). Furthermore, children with CNS tumors endorsed more discrepancies between what they would like to do and what they are able to do, especially regarding their physical functioning. Brain-damaged children are at three times the risk for psychological maladjustment compared children with chronic illness with no CNS involvement (Rutter, Graham, & Yule, 1970). Survivors of brain tumors are at increased risk for more severe deficits based on the more aggressive nature of their treatment (Butler & Copeland, 1993).

Type of Treatment

The type of treatment has been found to effect cognitive and psychological functioning. A loss of opportunity to learn, due to multiple clinic visits and side effects of treatment, may lead to learning problems in survivors.

Chemotherapy

On one hand, Copeland, Moore, Jaffe, and Culbert (1996) longitudinally studied 51 children with cancer who received ITC and 48 who received non-CNS treatments (NITC). Neuropsychological assessments included measures of intelligence, achievement, language, memory, distractibility, executive planning, fine-motor abilities, perceptual motor abilities, and tactile-spatial skills. Results indicated that the effects of

chemotherapy are minimal with the exception that children treated with ITC demonstrated more perceptual-motor deficits than children treated with NITC at three year and long-term follow-up evaluations. However, their performances were still in the average range.

On the other hand, children treated via ITC are at risk for developing nonverbal learning difficulties, potentially requiring special education services (Armstrong, Blumberg, & Toledano, 1999). Also, more intensive chemotherapy has been associated with more adjustment problems (Zebrack & Zeltzer, 2003). Moleski (2000) addressed a misconception that CNS chemotherapy treatment is safer than CRT. After reviewing available literature, Moleski concluded that CNS chemotherapy is harmful, cautioning that the late-effects are still largely unknown. All in all, cancers that require more aggressive treatment place children at an increased risk for cognitive problems (Winqvist et al., 2001; Armstrong et al., 1999; Fuemmeler et al., 2002).

Radiation Therapy

Within the neurocognitive domain, areas that may be affected by CRT include short-term memory, attention, fine motor coordination, visuospatial abilities, and somatosensory abilities (Lottick & Neglia, 2005). Nearly all children with brain tumors that are treated with high doses of CRT will need ongoing special education services. On one hand, Rubenstein et al. (1990) found that cognitive profiles in survivors of ALL were similar, regardless if they were treated with 1800 cGy or 2400 cGy of CRT. Therefore, findings suggest that the impact of CRT is an all-or-none phenomenon, opposed to a dose-dependent effect (Butler et al., 1994). On the other hand, Kieffer-

Renauz, et al. (2000) studied 36 survivors of medulloblastomas treated with radiation doses of either 25 Gy or 35 Gy. Results indicated that survivors treated with 25 Gy doses demonstrated higher overall intelligence, concluding that there is a negative correlation between strength of radiation dose and intelligence. Overall, chemotherapy drugs are preferential over radiation therapy for younger children, since the effects are greatest for younger children (Ulrich & Pomeroy, 2003).

Combination Therapy

Reimers, Ehrenfels, Mortensen, Schmiegelow, Sonderkaer, Carstensen et al. (2003) studied 133 adult survivors of childhood brain tumors treated with resection, chemotherapy, radiation therapy, or a combination of the three. Results indicated radiation therapy to be the most important predictor for cognitive deficits, as well as hydrocephalus, history of having a shunt, having a cerebral hemisphere tumor, and younger age at diagnosis.

Butler, Hill, Steinherz, Meyers, and Finlay (1994) studied the neuropsychological after-effects of CRT, intrathecal methotrexate (IT-MTX), and systemic methotrexate (SYS-MTX) in 120 pediatric cancer survivors. A comprehensive neuropsychological battery was administered to all subjects. Results revealed the detrimental effects of CRT on posterior, nondominant hemispheric abilities. Specifically, CRT in combination with IT-MTX had devastating effects on cognitive abilities, even when controlling for CNS cancer. Also, children treated with IT-MTX and CNS radiation therapy (CRT) have been documented to be at risk for experiencing more educational and employment barriers (Rouke & Kazak, 2005).

Bone Marrow Transplant (BMT)

Changes in neuropsychological capacity over time have been noted in children with ALL who were treated with a BMT, particularly in cognitive and motor skills (Parth, Dunlap, Kennedy, Ordy, & Lane, 1989). Achievement abilities, memory, and fine motor skills have also been found to be at risk for decline in BMT survivors (Cool, 1996). Children younger than the age of three and treated with total body irradiation demonstrate more cognitive deficits (Phipps, 2005). Kramer, Crittenden, DeSantes, & Cowan (1997) found a significant cognitive decline in survivors of BMTs one year post treatment, which remained stable up to three years post treatment. Authors concluded that these children are at risk for academic problems.

Age at Diagnosis

The age of diagnosis is an important contributor to both neurocognitive and psychosocial functioning. Vainionpaa (1993) suggested that younger, less developed bodies are more susceptible to cytotoxic therapy, causing greater mobility struggles than experienced by older children being treated for cancer. Children with medulloblastomas treated before the age eight demonstrated greater declines in their intellectual abilities, specifically nonverbal abstract reasoning, general fund of information, and overall intellectual ability than those treated over age eight (Palmer, Goloubeva, Reddick, Glass, Gajjar, Kun, et al., 2001). Children diagnosed with cancer before the age of five show more cognitive decline, memory deficits, and motor problems than children diagnosed after the age of five or six (Winqvist et al., 2001; Armstrong et al., 1999).

Children treated for a brain tumor before the age of six are at a greater risk for difficulties in educational and employment areas. Barrera, Wayland, Agnostino, Gibson, Weksberg, and Malkin (2003) reported that younger children demonstrated more externalizing behavior problems, hypothesizing that older children have more difficulties repressing their anger. In contrast, Koocher and O'Malley (1981) reported that psychosocial maladjustment was associated with older age of diagnosis. Overall, it appears younger age of diagnosis negatively influence neurocognitive functioning, while diagnosis in adolescence negatively influences psychosocial functioning in survivors.

Sex

Sex has also been documented as influencing psychosocial adjustment. For example, Langeveld et al. (2004) reported that female survivors of childhood cancer between the ages of 16 and 49 at least five years off-treatment endorsed more pathology overall than males, namely in the areas of physical functioning, overall health perception and pain, and mental health.

On the other hand, male survivors have been found to be more depressed and anxious, as well as less active, than female survivors (Chang, Nesbit, Youngren, & Robison, 1987). The direction and magnitude of the effects of sex on cancer treatment appears to be dependent on age, in addition to the type of injury and its location (Kadan-Lottick & Neglia, 2005).

Factors Associated with Better Psychosocial Functioning

Better psychosocial functioning has been associated with shorter treatment duration (Koocher & O'Malley, 1981), longer time since diagnosis (Cella & Tross, 1986),

and less functional impairment (Elkin et al., 1997). Concerning personal factors, better psychosocial functioning has been associated with better level of functioning before diagnosis (Kupst, Natta, Richardson, Schulman, Lavigne, & Das, 1995), lower level of personal distress (Last & Grootenhuys, 1998), and better cognitive functioning (Boman & Bodegard, 2000).

Previous Research in the Connection between Neurocognitive and Psychosocial Functioning

Eiser (2004) described the range of stressors dealt to children with cancer to include understanding their condition (diagnosis, treatment, and prognosis), adapting to treatment and its side-effects, relating to medical staff, identifying with family and peers, dealing with their medical and home world, and their feelings of being different. Eiser et al. (2000) described three areas in which psychosocial functioning has been measured in the field; namely, general mental health, lifestyles and health behaviors, and academic and cognitive functioning. That is, each of these three factors is important aspect to the quality of life of children surviving cancer.

Regardless of type of treatment, pediatric cancer survivors are at risk for academic decline, particularly in arithmetic abilities (Copeland, Moore, Francis, Jaffe, & Culbert, 1996). Butler and Copeland (2002) made the assertion that more neuropsychological deficits compromise academic success and, ultimately, the survivor's quality of life. Furthermore, academic functioning has been reported to be a contributing factor to the social functioning in survivors. To explain, Newby et al. (2000) demonstrated that academic functioning best predicted social skills in these children,

accounting for 20% of the variance in the child's social skills. Namely, more academic difficulties were associated with more psychological functioning difficulties as rated by both parents and teachers. Also, Boman and Bodegard (2000) found that better psychological functioning is related to less cognitive difficulties.

Purpose of Current Study

With the increase in survival rates, concerns have been raised of psychosocial quality of life in childhood cancer survivors. Research has gravitated toward studying these children as these children leave the hospital and return to their previous life.

Past literature has reported inconsistent findings concerning psychosocial functioning in childhood survivors. While several authors have hypothesized reasons this discrepancy occurs, there is still much to answer. Varni et al. (1998) suggest these discrepancies result from the heterogeneity of research participants and from characteristics such as age at diagnosis, intensity of treatment, and time since diagnosis. Furthermore, there is limited research in this area. Brandlyn et al. (1995) reported that only 3% of published clinical trials in pediatric oncology were found to include data related to issues of quality of life.

In addition, there are several facets encompassing quality of life, including general mental health, lifestyles and health behaviors, and academic and cognitive functioning (Eiser et al., 2000). One of these domains of quality of life that has been consistently documented as a significant risk for decline in childhood cancer survivors is cognitive functioning (Conglio & Blackman, 1995; Winqvist et al., 2001). Furthermore, survivors with more cognitive deficits have been found to have more adjustment

difficulties (Boman & Bodegard, 2000). Also, treatment variables, such as diagnosis and type of treatment, have been reported to influence both cognitive and psychosocial functioning in survivors (Armstrong et al., 1996; Lottick & Neglia, 2005, Reimers et al., 2003). Therefore, a connection has been established between psychosocial functioning, cognitive functioning, and effects of treatment variables.

However, more specific domains of cognitive functioning, such as neurocognitive abilities, have not been studied with regards to their effect on psychosocial functioning in pediatric cancer survivors. To this date, most studies researching these two factors have used broad measures of cognitive functions, such as the FSIQ from the Wechsler scales. Furthermore, treatment variables have not been explored in terms of how and to what extent they affect psychosocial functioning. Since survivors have been documented to have greater cognitive deficits and children with greater cognitive difficulties tend to have greater adjustment difficulties, this project evaluated the role that treatment and neurocognitive variables play in psychosocial functioning of pediatric cancer survivors. Exploring the relationship between specific treatment factors, neurocognitive abilities (opposed to broad cognitive ability) and psychosocial adjustment can illuminate specific areas in which intervention is most warranted.

Research Hypotheses

First, it is hypothesized that children treated with combination therapy will be at risk for more behavior problems compared to children treated with surgery or chemotherapy only. This anticipated outcome is consistent with previous findings by Reimers et al. (2003). Authors found radiation therapy to be the most important

predictor for cognitive deficits. Langeveld et al. (2002) discovered that children treated with IT-MTX and CRT are at risk for experiencing more educational and employment barriers. Hill, Kornblith, Jones, Freeman, Holland, and Glicksman (1998) found survivors of ALL treated with chemotherapy and methotrexate are at risk for psychological problems. Survivors treated with surgery and chemotherapy alone exhibit more positive neurocognitive outcomes (Copeland, deMoor, Moore, & Ater, 1999).

Second, it is hypothesized that children treated with a BMT will be at risk for more behavior problems compared to children treated with surgery or chemotherapy only. According to Vannatta (1998), peers have rated BMT survivors to have fewer friends, to be more socially isolated, and to be less physically attractive. Also, BMT survivors demonstrate declines in social competence, self-esteem, and emotional well-being (Phipps, 2005).

Third, it is predicted that survivors of brain tumors will demonstrate more behavior problems than survivors of ALL. This hypothesis is consistent with previous findings of Fuemmeler et al. (2002) and Mulhern et al. (1993) who reported that children diagnosed with brain tumors have more social competency deficits. Also, Rutter et al. (1970) found children with brain-damage are at three times more risk for psychological maladjustment compared to children with chronic illness with no CNS involvement. Furthermore, Eiser et al. (2004) reported that children with CNS tumors experience more quality of life difficulties compared to children with ALL and normal population means.

Fourth, it is hypothesized that children diagnosed with cancer in middle childhood (ages six to twelve) will demonstrate more behavior problems than children diagnosed before the age of six. This may be accounted for by the obstacles created by the cancer experience toward achieving a sense of identity and intimacy. Koocher and O'Malley (1981) reported older age at diagnosis to be associated with psychosocial maladjustment. Eiser (2004) reported that the cancer experience in adolescents creates obstacles to their achieving a sense of identity and intimacy.

Fifth, it is hypothesized that survivors with more neuropsychological deficits will be rated as having more behavior problems. Although Boman and Bodegard (2000) reported that less cognitive deficits are related to better psychosocial functioning. No previous research is available in this population regarding the relationship between neuropsychological variables and psychological functioning. Therefore, an exploratory analysis was conducted to examine these relationships.

CHAPTER II

METHOD

Participants

Participant demographic information and test data were obtained from an existing archival database comprised of patients of the Hematology/Oncology Center at Cook Children's Medical Center in Fort Worth, TX. Data was collected as part of a standard neuropsychological battery given to patients referred to the Center over the past five years who are on-treatment or off-treatment for cancer. The data from these files were archived in the Department of Psychology/ Neuropsychology at Cook Children's Medical Center. Survivors between the ages of three and twelve were selected who meet the following criteria: have finished treatment, have been administered all the selected measures, and meet the time since diagnosis criteria.

Participant characteristics are presented in Table 3. The total sample of 177 participants consisted of 107 males (61%) and 70 females (39%). Of the entire sample, 69 (39%) were diagnosed with acute lymphoblastic leukemia (ALL) and 108 (61%) were diagnosed with a brain tumor. The average time since diagnosis was 3.58 years, ranging from 2 to 13 years. The average time off treatment was 2.56 years, ranging between 1 and 13 years. The average age at diagnosis was 4.36 years, ranging from 0 to 12 years. Among the treatment modalities, 34 (19%) were treated via surgery only, 53 (30%) were treated via chemotherapy only, 23 (13%) were treated via bone marrow transplant (BMT), 67 (38%) were treated with a combination of treatments other than BMT.

Measures

Behavioral Assessment System for Children

The Behavior Assessment System for Children System (BASC™, AGS Publishing, www.agsnet.com) uses an approach to evaluating behaviors and self-perceptions of children ages 2.5 to 18 that is multimodal and multidimensional (Reynolds & Kamphaus, 1998). The BASC approach includes a comprehensive set of rating scales that are quick and easy to score, aiming to quantify the behaviors and emotions of children and adolescents.

This instrument includes symptoms from the *Diagnostic and Statistical Manual of Mental Disorders: Third edition-Revised* (DSM-III-R, American Psychiatric Association, 1997), helping with the diagnostic differentiation process in children and adolescents. Problem behaviors identified by the BASC are designed to be the focus of intervention. Adaptive skills are also identified, which can be integrated into interventions to improve the child's behavior. The BASC instrument is highly applicable in the pediatric population due to the connection between academic difficulties and adjustment problems, such as low self-concept or anxiety. Furthermore, the BASC identifies emotional disturbance.

Development

Originally, the authors wrote definitions of behaviors to be reviewed by psychologists and doctoral students. After definitions were established, professionals with experience in several different areas wrote items, including psychology, psychiatry, and teaching. This instrument went through two different tryouts before the final item selection for teachers, parents, and students to complete was finished. The final

standardization sample was collected from 116 testing sites across the United States, including schools, preschools, and daycare centers. For example, in the sample for the parent rating scale (PRS) for ages 6-11 years, the sample included 1,027 females and 1,057 males. The race/ethnicity breakdown included 139 African American, 96 Hispanic, 1,815 White, and 34 Other.

Normative Sample

Clinicians were given the choice of normative samples: general, female, male, or clinical. The general sample was representative of a large national-based sample regardless of sex, race, special education classification, or parent education levels. The Female and Male normative samples were derived from the general sample. This sample allowed the clinician to separate out behaviors that are unusual for a child's age and sex. Finally, the clinical Norms, available for ages four and older, compared the individual's responses to a population of children and adolescents with psychopathology. When a child's responses are extremely elevated compared to the general sample, using the clinical norms are indicated (Reynolds & Kamphaus, 1998).

Validity Scales

Validity scales were provided to detect threats to validity, including carelessness, failure to attend to item content, portrayal of the child in overly positive or negative light, lack of motivation, or poor comprehension. Also, emotional disturbances or limited knowledge of the child being evaluated can limit validity of the informant's responses. For the parent rating scale (PRS), the f-scale ("fake bad") identified response sets that are excessively negative, based on items that were infrequently endorsed in the

standardization sample. If the f-scale is high, the respondent is attempting to make the child look bad, or the child actually does have a large number of serious behavioral or emotional problems. The scales have high internal consistency and test-retest reliability.

Forms

There are three different forms: the parent rating scale (PRS), the teacher rating scale (TRS), and the self-report rating scale (SRS). For the purposes of this project, only the PRS was used. The PRS is a useful instrument in measuring both adaptive and problem areas in the home setting. It has three different forms for different age groups, including pre-school, child, and adolescent. The PRS is appropriate for ages two to 18 years. It takes approximately 10-20 minutes to complete and has a four choice response format.

Composite Scales

The PRS scales can be divided into either clinical or adaptive scales. Within the clinical scales, maladaptive behaviors are assessed. Clinical scales include aggression, anxiety, attention problems, atypicality, conduct problems, depression, hyperactivity, somatization, and withdrawal scales. Clinical scales are not provided for ages 2 to 3.11. Composite scores are also derived to summarize the child's performance, including the child's adaptive and maladaptive behaviors. Adaptive scales include adaptability, social skills, leadership, activities of daily living, and functional communication.

The externalizing problems composite score is a composite of the hyperactivity, aggression, and conduct problems scales. This composite measures disruptive behavior problems, as well as uncontrolled behaviors. Adults readily see these behaviors because

the child may be more unresponsive to adult direction and disruptive (Reynolds & Kamphaus, 1998).

The internalizing problems composite consists of the anxiety, depression, and somatization subscales. This composite score measures anxiety, depression, and similar areas of concern that are not marked by acting out behaviors. These types of behaviors may not be as noticeable as externalizing behaviors since the child may not be disruptive (Reynolds & Kamphaus, 1998).

The behavior symptoms index (BSI) is a composite score that provides an overview of problematic behaviors since it is derived from a combination of central scales. Contributing scales include aggression, hyperactivity, anxiety, depression, attention problems, and atypicality. The BSI provides valuable information and can aid in determination of the global assessment of functioning (GAF) from the *DSM* manuals (Reynolds & Kamphaus, 1998).

The adaptive skills composite for the PRS includes adaptability (ages 2.5 to 11 only), leadership (ages 6 to 18 only), and social skills (all ages) scales. This composite score indicates how well the child adapts to changes in their environment, their ability to interact with peers and adults in a variety of settings, and how their skills associate with working with others (Reynolds & Kamphaus, 1998).

Interpretation of Composite Scores

BASC composite scores are represented as *T*-scores ($M = 50$, $SD = 10$). Clinical maladjustment is indicated at *T*-scores above 70 for clinical scales and *T*-scores below 30 for adaptive scales. For clinical scales, at-risk ranges consist of *T*-scores between 60

and 69. For adaptive scales, at-risk *T*-scores range from 31-40. Average scores range from 59 or lower and 41 or higher for adaptive scales. In the event a child has significant problems, their scores may ceiling when compared to general norms (Reynolds & Kamphaus, 1998).

Validity of the BASC

Factor and structural equation analyses for the externalizing and internalizing composite scales have supported construct validity. The BASC correlates highly with the Child Behavior Checklist (CBCL™; Achenbach System of Empirically Based Assessment, <http://www.aseba.org>, Achenbach, 1991), and moderately with the Personality Inventory for Children – Revised (PIC-R™; Western Psychological Services, <http://www.wpspublish.com>, Lachar, 1990). The BASC system may actually be superior to the CBCL and has generally good reviews (Adams & Drabman, 1994; Gladman & Lancaster, 2003). Furthermore, construct validity was documented in the following clinical groups: conduct disorder, depression, Attention Deficit Hyperactivity Disorder, mild mental retardation, and autism (Reynolds & Kamphaus, 1998).

Reliability of the PRS

The internal-consistency for the PRS composite scores range from the middle .80s to low .90s at each of the three different levels, with reliabilities for the BSI ranging from .88 to .94. Overall, these composite scores are highly reliable, suggesting they are measuring the same domain of behavior (Reynolds & Kamphaus, 1998). The median test-retest reliability values are .85, .88, and .70 for each of the three different age ranges. Attention Problems, social skills, hyperactivity, and depression scales are

the most reliable subscales, with atypicality and conduct problems composite scales have relatively low reliability. The inter-parent reliability for the PRS composite scores are moderate, varying between .46, .57, and .67 for each of the three different age ranges (Reynolds & Kamphaus, 1998).

NEPSY: A Developmental Neuropsychological Assessment

The *NEPSY*® (Harcourt Assessment, www.harcourtassessment.com), originally the *NEPS*, was developed in 1980 in Finland as a brief assessment for children ages 5.0 to 6.11 years (Korkman, 1980). Further test development resulted in the addition of new subtests (Benton, Sivan, Hamsher, Varney, & Spreen, 1983). Subtests with poor reliability were eliminated and new items were added to adapt the instrument to a wider age range. The standardization sample consisted of 1,000 children between the ages of 3.0 and 12.11 years, which were then stratified for race and ethnicity, gender, parent education, and geographical region (Kemp, Kirk, & Korkman, 2001). Validation studies were conducted on clinical samples. Korkman, Kirk, and Kemp then published the *NEPSY* in 1998 as a developmental neuropsychological assessment. All the subtests of the *NEPSY* were standardized on the same, fully represented standardization sample (Kemp et al., 2001).

Alexander Luria's Theory

This instrument was founded in the theory of A.R. Luria (Luria, 1963). Luria conceptualized four interconnected levels of neurocognitive disorders and brain/behavior relationships: the structure of the brain, the functional organization of the brain based on structure, syndromes and impairments arising from brain disorders,

and clinical methods of assessment (Kemp et al., 2001). Luria divided the brain into three blocks: block I includes structures such as the diencephalon, brainstem, and medial regions of each hemisphere, responsible for life-sustaining activities, such as respiration and heartbeat, as well as attention necessary for cognitive functioning. Block II includes the posterior cortex, involved in information encoding and processing, as well as associating incoming information with past experience. Block III includes the frontal lobes, which regulate executive functioning, including behavior regulation, problem solving, and sequencing. Block III is affected both by the attentional processes of Block I and the information processing functions of block II (Kemp et al., 2001).

Blocks I, II, and III all play an integrative role in facilitating neurocognition. Impairment in one subcomponent of a certain function will not only influence other components contributing to more complex functions, but may also negatively affect the development of successive subcomponents of that function. Therefore, the NEPSY instrument measures these basic and complex subcomponents that comprise more complex capacities within different functional domains (language, memory, etc.; Kemp et al., 2001).

Purpose of the NEPSY

The NEPSY was developed as a well validated and reliable instrument designed to identify subtle impairments in different domains that can highlight areas that can impede learning. Other purposes of the NEPSY are to assess the influence of congenital or acquired brain damage and their affect on development and to aid in determining normal and atypical brain development in children. The NEPSY was also developed for

long-term follow-up monitoring in children with congenital and acquired brain damage (Korkman et al., 1998).

Core Domains and Subtests

This instrument assesses five different areas of functioning: attention/executive functioning, language, sensorimotor, visuospatial, and memory and learning. For purposes of this study, only the core subtests will be assessed. Different core subtests are administered based on the age of the child (see Table 1 for subtests). The NEPSY takes about two hours to administer to school-aged children (Ahmad and Warriner, 2001). Domains scores are calculated as standard scores ($M = 100$, $SD = 15$).

The attention/executive functioning core domain measures several facets, including executive functions (Tower, ages 5 to 12), simple, selective, and auditory attention (Auditory Attention, ages 5 to 12), response set shifting (Response Set, ages 5 to 12), visual attention (Visual attention, all ages), and basic motor persistence (Statue, ages 3 to 4; Korkman et al., 1998). A word of caution: Ahmad and Warriner (2001) warn that the domain of attention/executive Functioning should be examined carefully, as some reviews warn that it may not be possible to measure “executive functioning” in young children.

The language core domain measures different areas of language, including naming abilities (Body Part Naming, ages 3 to 4); auditory discrimination and phonological awareness (Phonological Processing, all ages), rapid access to alternating language labels (Speeded Naming, ages 5 to 12), and receptive language (Comprehension of Instructions, ages 5 to 12; Ahmad and Warriner, 2001).

The sensorimotor core domain aims to measure dexterous finger movements (Finger Tapping, ages 5 to 12), kinesthetic praxis and tactile processing (Imitating Hand Positions, all ages), and graphomotor speed and accuracy (Visuomotor Precision, all ages; Ahmad and Warriner, 2001). The visuospatial Processing Core domain assesses abilities to integrate visuospatial input and motor output (Design Copying, all ages), to judge line orientation (Arrows, ages 5 to 12), and to reproduce three dimensional block constructions from models (Block Construction, Core ages 3 to 4, Expanded ages 5 to 12; Ahmad and Warriner, 2001).

The memory and learning core domain assesses immediate and delayed memory for faces (Memory for Faces, all ages), immediate and delayed memory for names (Memory for Names, all ages), verbal memory (Narrative Memory, all ages) and auditory short term memory (Sentence Repetition, Core ages 3 to 4; Expanded ages 5 to 12; Ahmad and Warriner, 2001).

Reliability and Validity

The average reliabilities for the 5 to 12 age group range from 0.79 to 0.87 for all five functional domains (Anastasi & Urbina, 1997). Korkman et al. (1998) administered the NEPSY to 168 children on two separate occasions, concluding that the stability coefficients range from 0.68 (attention/executive Function) to 0.90 (Memory and Learning). Correlation between the NEPSY and academic grades was low (Korkman et al., 1998). Moderate correlations have been documented with other neuropsychological measures (Korkman et al, 1998).

Ahmad and Warriner (2001) warned that validity estimates of the NEPSY may be premature and much more research needs to be generated in this area. Kemp et al. (2001) cited a few limitations of this instrument, including that the subtests are not highly correlated with the general domain scales, partly because the instrument was developed based on theory and not factor analysis. Authors also stated that it is cumbersome to score (Kemp et al., 2001).

Procedure

Data from an anonymous archival data set including the BASC and NEPSY instruments for children diagnosed with ALL or brain tumors were assessed. Type of diagnoses, age at treatment, and type of treatment were also collected from the database. Criterion for inclusion also required the children to be off-treatment and the evaluation to have been conducted at least two years post-diagnosis. For patients that had received multiple evaluations, their first evaluation, assuming it was at least two years post-diagnosis, was selected.

The type of treatment the child received was categorized into one of four groups: neurosurgery only, chemotherapy only, combination of treatments, or bone marrow transplant (BMT). The combination of treatments category included a mixture of any combination of the following: neurosurgery, chemotherapy, and radiation therapy. Diagnoses were classified as either brain tumor or ALL. Children with other diagnoses, including Wilm's tumor, acute myelogenous leukemia (AML), hemophagocytic lymphohistiocytosis, static encephalopathy, Hurler's Syndrome, Hodgkin's lymphoma, traumatic brain injury, aplastic anemia, and sickle cell anemia

were excluded from this study. Cases in which the child's diagnosis or type of treatment was unavailable were also excluded. Age at diagnosis was classified into one of four groups: less than one year, one year to three years, three years to six years, and six years to twelve years.

The neurocognitive factors consisted of the five NEPSY composite factors from the NEPSY, including attention/executive functioning, language, sensorimotor, visuospatial, and memory/learning. The NEPSY factors were categorized into one of four groups based on the clinical classifications denoted by Kemp et al. (2001, see Table 1 and 2 for NEPSY core subtests for different ages). Standard scores above 91 represented the non-impaired, "at expected level" group, characterizing percentile ranks greater than the 26th percentile in the normative sample. The second category represented standard scores in the "slightly below expected level" range, accounting for percentile ranks between the 11th and 25th percentile. Standard scores within this range include 82 to 90.

The third category represented scores in the mild to moderately impaired level, referred to as "below expected level" by Kemp et al. (2001). Standard scores falling within this impairment group range between 70 and 81, accounting for percentile ranks between the 3rd and 10th percentile. The fourth category represented the severely impaired group, also referred to as "well below expected level" by Kemp et al. (2001). Inclusive standard scores range from 69 and lower, representing the 2nd percentile ranks and lower. The dependent variable, the BSI composite score from the BASC,

remained continuous. This scale, discussed as an overview of problematic behaviors, is a combination of clinical scales from the BASC.

Data Analysis

Standard procedures for assuring normality, linearity, multicollinearity, homogeneity of variances, and describing the population were performed. A conservative approach was used in data analysis such that only participants who completed all of instruments were included in the analysis.

Univariate descriptive analyses were performed on demographic and treatment variables. A one-way analysis of variance (ANOVA) with Tukey's honestly significant difference (HSD) test was conducted to determine the mean difference between type of treatment and behavior problems and the effect of age at diagnosis on behavior problems. An independent sample *t*-test was conducted to determine the relationship between diagnosis and behavior problems. A univariate ANOVA was performed, entering the coded NEPSY variables as factors and the BSI as the dependent variable. Welch's statistic was used to test the homogeneity of variance assumption because it is more sensitive to unequal group sizes than Levene's statistic (Garson, n.d.).

An analysis of covariance (ANCOVA) could not be performed for this analysis for several reasons. First, covariates in an ANCOVA model should be continuous (Garson, n.d.). Since type of treatment and diagnosis are categorical, these variables were not appropriate covariates for an ANCOVA model. Furthermore, age at diagnosis was not significantly correlated with the BSI, therefore was also not included in the ANOVA model.

Therefore, a post hoc hierarchical multiple regression was conducted to determine to what degree treatment variables (type of treatment, diagnosis, and age at diagnosis) and neuropsychological variables (attention/executive functioning, language, sensorimotor, visuospatial, and memory and learning) accounted for variance in overall behavior problems. Treatment variables were entered simultaneously in the first block. Then, the treatment variables were entered into the second block as covariates, followed by the five neuropsychological variables. The dependent variable was the overall composite for problematic behaviors, as measured by the BSI.

Finally, odds ratio analyses were performed on the treatment and neuropsychological variables in order to observe the likelihood of survivors to demonstrate more behavior problems than not. The median of the BASC BSI standard scores were calculated to use as the reference point to examine which survivors demonstrate more problematic behaviors than the others. The median was also used as the reference point for the neuropsychological factors.

CHAPTER III

RESULTS

For all demographic and treatment categorical variables, counts and percentages are provided in Table 3. Means and standard deviations for the behavior symptom index (BSI) from the Behavior Assessment System for Children (BASC) are also presented in Table 3. For each of the five neurocognitive domains, counts and percentages are presented in Table 4. The correlation matrix for all variables is presented in Table 5. An alpha level of .05 was used for all statistical tests.

An independent samples *t*-test was conducted to determine the relationship between type of diagnosis and problematic behaviors. The homogeneity of variance assumption was met, Levene's statistic, $F = 1.46$, $p = .23$. Results indicated that children diagnosed with acute lymphoblastic leukemia (ALL, $n = 69$, $M = 48.71$) demonstrate more behavior problems than children diagnosed with brain tumors ($n = 108$, $M = 46.03$), $t(175) = 2.24$, $p = .03$. The mean difference between the ALL and brain tumor sample was 2.68 points. The odds ratio analysis for ALL compared to brain tumor survivors was statistically significant, odds ratio = 1.88, $CI = 1.02$ to 3.49 , $p = .04$.

A one-way analysis of variance (ANOVA) was performed to test differences between type of treatment and behavior problems. The homogeneity of variances assumption was met, Levene's statistic, $F = 1.63$, $p = .18$. The omnibus test of the main effect of type of treatment was statistically significant, $F(3, 173) = 4.88$, $MS = 283.25$, $p < .01$. Tukey's honestly significant difference (HSD) test revealed survivors

treated with chemotherapy ($n = 53$) showed more behavior problems than those treated with neurosurgery only ($n = 34$), $SE = 1.67$, $p = .01$, $CI = 0.94$ to 9.63 . Children treated with a combination of treatments ($n = 67$) demonstrated more behavior problems than children treated with neurosurgery alone ($n = 34$), $SE = 1.60$, $p < .01$, $CI = 1.01$ to 9.33 . Survivors of BMT ($n = 23$) exhibited more behavior problems than survivors of neurosurgery only ($n = 34$), $SE = 2.06$, $p < .01$, $CI = 1.25$ to 11.92 . No other significant differences were found between treatment groups and behavior problems. The odds ratio analysis for surgery compared to other treatments was statistically significant, odds ratio = $.25$, $CI = .11$ to $.59$, $p < .01$. None of the odds ratio analyses for the other treatment variables were statistically significant.

A one-way ANOVA was conducted to determine the relationship between age at diagnosis and behavior problems. The homogeneity of variances assumption was met, Levene's statistic, $F = .90$, $p = .45$. The omnibus test of the main effect of age at diagnosis was not statistically significant, $F(3, 173) = .75$, $MS = 46.52$, $p = .52$.

A univariate ANOVA was conducted to uncover the main effects and interaction effects between neurocognitive variables and overall behavior functioning (see Table 6). The homogeneity of variances assumption was met for attention, Welch's statistic, $F = 1.58$, $p = .20$, language, Welch's statistic, $F = 1.17$, $p = .33$, sensorimotor, Welch's statistic, $F = .10$, $p = .96$, visuospatial, Welch's statistic, $F = .30$, $p = .83$, and memory and learning, Welch's statistic, $F = .12$, $p = .95$. A significant omnibus test of the main effect was found for attention and behavior problems, $F(3, 105) = 6.62$, $MS = 288.48$, $p < .001$. Tukey's HSD test revealed that survivors with severe ("way below expected

level") attention deficits ($n = 29$) demonstrate more behavior problems than those with average ("at expected level") attention skills ($n = 86$), $SE = 1.42$, $p = .04$, $CI = .18$ to 7.58 and low average ("slightly below expected level") attention abilities ($n = 39$), $SE = 1.62$, $p = .04$, $CI = .18$ to 8.63 . The main effect of language and behavior was significant, $F(3, 105) = 2.93$, $MS = 127.92$, $p = .04$. However, none of the simple main effects were statistically significant. The effect of sensorimotor abilities was not statistically significant, $F(3, 105) = .99$, $MS = 42.95$, $p = .40$. The effect of visuospatial abilities was not statistically significant, $F(3, 105) = 1.61$, $MS = 70.36$, $p = .19$. The effect of memory was not statistically significant, $F(3, 105) = .64$, $MS = 27.97$, $p = .59$. None of the odds ratio analyses for the neuropsychological variables were statistically significant.

A post hoc hierarchical multiple regression was conducted to predict behavior problems from treatment variables and neuropsychological variables. The model included all neuropsychological variables and treatment variables, identifying the treatment variables as covariates to control for their effects on the relationship between neuropsychological factors and problematic behavior. Results for the model were significant, $F(8, 168) = 2.90$, $p < .01$. The model accounted for 12% of the variance in behavior problems ($R Square = .12$). After controlling for the effects of the treatment variables, visuospatial functioning also emerged as a significant neuropsychological predictor of behavior problems, $\beta = -.22$, $t = -2.35$, $p = .02$. Type of treatment was also a significant predictor, $\beta = .20$, $t = 2.59$, $p = .01$. Diagnosis was a significant predictor, $\beta = -.17$, $t = 2.03$, $p = .04$. The attention factor was close to significance, β

$= .17, t = 1.90, p = .06$. There were no other variables in the model that were statistically significant. Results for the regression are displayed in Table 7.

CHAPTER IV

DISCUSSION

Results support the hypotheses that survivors treated with combination of chemotherapy, radiation therapy, or neurosurgery and bone marrow transplant (BMT) demonstrated more behavior problems than children treated with neurosurgery alone. This finding is also consistent with studies conducted by Eiser et al. (2004), Reimers et al. (2003), Moleski (2000), Armstrong et al. (1999), and Kramer et al. (1997) which examined the effect of treatment variables on psychosocial functioning.

Possible explanations for differences in the effects of type of treatment may be due to the neurotoxic effects of chemotherapy and radiation therapy. Both chemotherapy and radiation therapy have both been found to cause brain calcifications and impede white matter development in survivors (Moore, 2005). White matter loss has been associated with cognitive deficits (Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000), as well as problems in speed of processing, memory, and executive functioning (Gunning-Dixon & Raz, 2000). Children with cognitive difficulties, such as with processing information and memory, may have more difficulty with emotional responses which could likely be affecting how they process and respond negative emotions behaviorally (Boman & Bodegard, 2000).

Mulhern, Merchant, Gajjar, Reddick, and Kun (2004) reported that children treated by neurosurgery alone demonstrate less severe declines in their intellectual abilities than other treatment modalities. Consequently, this implies that survivors treated with chemotherapy and/or radiation therapy are experiencing more cognitive

deficits, as found in this study, and thus are at an increased risk for psychological difficulties (Boman & Bodegard, 2000).

In fact, the effect of type of treatment is quite influential throughout this study. To explain, this study finds child survivors of ALL are 1.88 times more likely to demonstrate behavioral problems than survivors of brain tumors. Researchers hypothesize treatment type is largely responsible for behavioral differences observed between these two groups. That is, neurosurgery is often the primary treatment for survivors of brain tumors (Tomita, 2000). If additional therapies are required, their efficacy is enhanced with more complete the resection (Ater et al., 2005). On the other hand, the length of treatment and aggressiveness of therapy doses differ in the ALL population. That is, the typical treatment duration for children with ALL is typically longer, ranging between two and a half to three years (Margolin et al., 2001). Children treated via BMTs, typically ALL survivors in this study, are treated with high doses of chemotherapy and radiation therapy (Kurtzberg & Clements, 2006). Thus, children treated with neurosurgery only (i.e. brain tumor survivors) demonstrate 25% less behavioral problems.

Contrary to prediction in this study, older age at diagnosis is not significantly related to behavior problems. However, since the neuropsychological instrument chosen for this evaluation is designed for children between the ages of three and twelve, children outside this age range were not included in this study. Age exclusion may have potentially confounded the relationship between age at diagnosis and behavior problems. Research has documented that adolescents are more at risk for behavior

problems. Shelby, Nagle, Barnett-Queen, Quattlebaum, and Wuori (1998) found that adolescent survivors of ALL exhibited more deficits in their adaptive behaviors and more internalizing behavior problems than elementary-age survivors. Furthermore, researchers found adolescents to have a higher risk for social maladjustment in comparison to other ages (Poggi et al., 2005). Also, Poggi et al. (2005) found that longer time since diagnosis was related to more cognitive and psychological impairment. Therefore, it is possible that this sample of survivors may exhibit more impairment in time. Overall, this adolescent population is certainly of interest and will benefit from further study.

Concerning neuropsychological factors, survivors in this study exhibit more neuropsychological deficits compared to the NEPSY normative sample. Visuospatial functioning is predictive to behavioral difficulties in survivors. This finding is consistent with that of Copeland (1992), which found ALL survivors treated with cranial radiation therapy (CRT) experience significant difficulties with visuospatial organization compared to the control group. Second, attention abilities influence behavior problems in this study and significant deficits in attention may predispose children to more problems in their behavior. Finally, survivors' language abilities affect their psychosocial functioning.

It is important to note that attention and language factors are highly correlated, a finding consistent with Tirosh and Cohen's (1998) conclusions. Tirosh and Cohen (1998) discovered significant incidence of language deficits in a sample of children with attention difficulties. Therefore, it seems the survivor's psychological functioning is

susceptible to a mutually shared characteristic in the language and attention factor scores, such as listening skills that could affect both language and attention abilities.

Based on these results, the effects of type of treatment and neuropsychological variables on psychosocial health lie on a continuum. Children treated with neurosurgery only are at one end of this continuum, exhibiting minimal visuospatial, attention, and language deficits and thus fewer behavior difficulties. As children receive therapies in addition to neurosurgery, such as neurosurgery with chemotherapy and/or radiation therapy, chemotherapy only, or BMTs, they are more likely to demonstrate more attention, visuospatial, and language deficits and subsequent behavior problems.

Overall, it is concluded that there are additional factors affecting behavior in this population that were not accounted for in this study, in addition to type of treatment and neuropsychological functioning, such as child, family, and environment factors, as also proposed by Last and Grootenhuis (1998) and Hill et al. (2003). Davies (2004) listed several factors related to resiliency in children and are listed as follows: easy temperament, internal locus of control, positive self-esteem, and active coping style. The child's temperament, referred to as "biologically based personality traits that affect the child's orientation to the world" (Davies, 2004, pp. 70) may certainly be a mediating factor in the relationship between neuropsychological, treatment, and psychosocial functioning. The child's temperament and the psychological adjustment in mothers of children with cancer are two crucial predictors of the psychological health in the survivors (Barrera et al., 2003).

The literature shows a link between parental health and psychological functioning in survivors, as proposed by Kazak et al. (1997), who found family variables may influence psychological adjustment. Kazak and colleagues examined 130 mothers of childhood leukemia survivors, reporting a prevalence of severe Posttraumatic Stress Disorder (PTSD) in 10.2% of mothers, as compared to 2.8% in the comparison group of 148 mothers of healthy children. Researchers found that posttraumatic symptoms in parents of childhood cancer survivors are related to more communication problems and reports of less satisfaction in the family. Drotar (1997) indicated psychological adjustment in mothers of cancer survivors directly influences the child's psychological functioning. Furthermore, children of parents with mental illness may display difficulties with emotional regulation, poorer self-concepts, or insecure attachments with their parents (Davies, 2004). Researchers found higher family adaptability and cohesiveness (Newby et al., 2000) and open communication in the family (Kupst & Schulman, 1988) to account for less of behavior problems in child cancer survivors.

The literature also supports environmental variables that may also be influencing the relationship between type of treatment, neuropsychological functioning, and psychosocial functioning in this study. In children who sustained severe traumatic brain injuries, six-month and one-year follow-up evaluations found socioeconomic status (SES) to be a mediating factor in posttraumatic stress symptoms in survivors (Levi, Drotar, Yeates, & Taylor, 1999). Children living in poverty are more likely to score lower on cognitive and academic tests, exhibit externalizing behaviors, be exposed to environmental toxins and violence in the community, and have difficulty accessing

proper health care services (Davies, 2004). On the contrary, Butler et al. (1999) discovered contrary findings that SES is not a consistent predictor of psychological functioning in childhood cancer patients and survivors.

Limitations of the Study

Numerous limitations are noted in this study. First, no comparison group was included. Winqvist et al. (2001) stated that a comparison group is essential in pediatric oncology research. Zebrack and Chesler (2002) cautiously interpreted their findings due to the lack of comparison group in their study. Shelby et al. (1998) recommended the use of demographically matched comparison groups of healthy children and other chronically ill children.

Secondly, concerning treatment variables, the types of chemotherapeutic and radiation drugs used to treat the participants were unavailable, as well as their doses. Furthermore, the method of administration of the treatments was unknown. Adjustment difficulties have been linked to more intensive chemotherapy treatment (Zebrack & Zeltzer, 2002 review). Higher doses of radiation therapy may also place the child at more risk for intellectual deficits (Mulhern & Palmer, 2001). Therefore, it is recommended for future studies to account for this information when researching these variables to determine their potential contribution of the relationship.

Third, any medication the child may have been taking was unavailable. Medications the child was taking, such as psychostimulants or corticosteroids may have influenced the expression of both neurocognitive and psychosocial functioning. The presence of psychostimulants could potentially increase performance on the cognitive

scales (Brown & Sawyer, 1998). Mulhern et al., (2004) reported methylphenidate, a common psychostimulant, has positive effects on sustained attention and vigilance, and perhaps on social relationships. Psychiatric side-effects of corticosteroids may include hypomania, mood swings, sleep difficulties, anxiety, and personality changes (Brown, 1998). Dexamethasone therapy, a corticosteroid, may increase the risk for neurocognitive late effects in children treated for ALL (Brown, 1998).

Recommendations for Future Research

Based on the results from the current study, it would be beneficial to study the individual clinical scales of the Behavior Assessment System for Children (BASC) to determine the exact effects of type of treatment, diagnosis, and neuropsychological functioning on internalizing and externalizing behaviors. The dependent variable, the behavior symptom index (BSI) represented an overall composite of the clinical scales on the BASC. However, the BSI only answers whether the child's behavior is worse than their peers' behavior. While the clinical scales were beyond the scope of this study, Reynolds and Kamphaus (2002) discuss that the use of composite scores is limited and do not provide as good of benefits as the individual scales.

Furthermore, this study illustrates that the attention, visuospatial, and language factors from the NEPSY influence psychosocial functioning in survivors. However, the individual scales that comprise these factor scores were not available for analysis. Researching these individual subtests is imperative to understanding their effect on psychosocial health. To explain, the attention factor also incorporates measurements of executive functioning which makes it difficult to disentangle which contributes more to

that factor. Additionally, the language factor measures both expressive and receptive language skills. Based on the composite factor scores, it is difficult to determine which of these areas is most affecting psychological health in survivors.

Several studies have emphasized the importance of obtaining information from multiple informants. Bradlyn, Ritchey, Harris, Moore, O'Brien, Parsons, et al. (1996) proposed a multifaceted definition of quality of life for children (QOL) with cancer;

QOL in pediatric oncology is multidimensional. It includes, but is not limited to, the social, physical, and emotional functioning of the child or adolescent, and when indicated, his/her family. Measurement of QOL must be from the perspective of the child, adolescent, and family, and it must be sensitive to the changes that occur throughout development. (p.1333-4)

Therefore, it is recommended for additional studies to include measures from parents, teachers and the child themselves.

Likewise, longitudinal studies would illuminate the long-term effects of these relationships. While this study included participants at least two years post diagnosis, the years since the child was diagnosed ranged from two to thirteen years. While 40% of the evaluations occurred two years post diagnosis, the range in years since diagnosis may be a confound variable in this study. That is, numerous studies have documented a decline in intelligence over several years (Mulhern et al., 2004). In survivors of posterior fossa brain tumors, researchers found a gradual decline in intellectual abilities over a four year time period, averaging two points during the early phase of treatment (Spiegler, Bouffet, Greenberg, Rukta, & Mabbott, 2004). Palmer, Gajjar, Reddick, Glass,

Kun, Wu, et al. (2003) found survivors of medulloblastomas treated with radiation therapy lost 2.2 intelligence points per year over a seven-year study period.

Finally, the results from this study suggest that there are variables not accounted for in this study that are affecting psychosocial functioning in survivors. The factors discussed in the previous section, including child, family, and community variables, include essential factors that may be influencing the effects of the cancer experience on the child. Future studies need to explore variables to determine their effect on both neurocognitive and psychosocial functioning.

Implications for Practice

There are numerous implications of this study. This study explains some of the discrepancy in findings in the psychosocial literature. Results of this study suggest that, to some extent, type of treatment and diagnosis, as well as attention, visuospatial, and perhaps language deficits influence later development of behavior problems. While children have been repeatedly found to demonstrate substantial neuropsychological deficits, it appears there are other factors in addition to neuropsychological functioning that are affecting their quality of life. This study provides evidence to the importance of looking at other factors that may place survivors at risk for developing psychosocial difficulties. Though several studies have found that these survivors are functioning well psychologically (Zebrack & Chesler, 2002; Eiser et al., 2000; Mulhern et al., 1993; Elkin et al., 1997), others have reported later problems with intimacy, being teased, finding employment, etc. (Kazak et al., 1997; Rourke & Kazak, 2005; Boman & Bodegard, 1995).

Also, attention, language, and visuospatial abilities are predictive variable of behavior problems in this study, regardless of treatment variables. Returning to school for survivors is already stressful due to the change in their physical appearance (Spirito et al., 1991) and difficulties in social relationships may compound this stress (Butler et al., 2001). Thus, survivors may be struggling with difficulties in their educational, social, and psychological worlds.

In all, it is imperative to help the child easily transition into his 'everyday life' while observing for latent aftereffects. This research provides justification for screening survivors for neuropsychological and psychosocial difficulties as they are returning to school. This study highlights several areas to be cognizant of when working with survivors. Perhaps cognitive rehabilitation programs can incorporate a psycho-educational component in order to target potential survivors who are experiencing both neurocognitive and psychosocial difficulties.

There has been an effort in the pediatric oncology field toward positive psychology. Phipps (2005) suggests the field of psycho-oncology focus on factors that contribute to the healthy functioning of survivors rather than spending research efforts to discover the difficulties they are having. Past research has tended to focus on the assessment of maladjustment, rather than coping, adaptation, and resilience (Chang, 1991; Eiser & Havermans, 1994). Therefore, this study implies that children treated with surgery only and those who demonstrate average to above average attention and language abilities are less at risk for developing psychological difficulties. Further, this study insinuates that perhaps neurocognitive deficits alone do not significantly affect

how these children are functioning when they leave the hospital and return home and to school.

Perhaps the factors discussed by Hill et al. (2003), such as encouragement from the parents and teacher involvement, are in fact compensating for actual deficits in some of these children. In addition to the need for more research in this area as discussed above, improving the relationship between parents and teachers and working on the parent-child relationship could be very useful tools to include in rehabilitation programs.

Mulhern and Palmer (2001) suggest that psychologists follow an explicit plan to formally assess cancer survivors at set times to survey for known neurocognitive deficits or problems they may be at risk of developing. The present study indicates several factors that may place survivors at risk for developing psychosocial difficulties, namely type of treatment, as well as attention, visuospatial, and language deficits. As suggested by the present study, established psychosocial problems or risk factors for developing psychosocial difficulties should also be included in this prospective plan of assessment. Therefore, by more specifically addressing the comprehensive needs of this population, these children can be better facilitated to an easier recovery.

Table 1

NEPSY Core Subtests for Ages 3 to 4

Domain	Subtests
Attention/executive functioning	Visual attention
	Statue
Language	Body part naming
	Phonological processing
Sensorimotor	Imitating Hand Positions
	Visuomotor Precision
Visuospatial	Design copying
	Block construction
Memory and learning	Memory for faces
	Memory for names
	Narrative memory
	Sentence repetition

Table 2

NEPSY Core Subtests for Ages 5 to 12

Domain	Subtests
Attention/executive functioning	Tower
	Auditory attention and response set
	Visual attention
Language	Phonological processing
	Speeded naming
	Comprehension of instructions
Sensorimotor	Imitating Hand Positions
	Visuomotor Precision
	Fingertip tapping
Visuospatial	Design copying
	Arrows
Memory and learning	Memory for faces
	Memory for names
	Narrative memory

Table 3

Demographic and Dependent Variable Summary (N = 177)

Variables	Mean	Standard deviation	Range
Age at dx	4.36	2.95	0 - 12
Years since dx	3.58	1.89	2 - 13
Years off tx	2.56	1.96	1 - 13
BASC BSI	47.07	7.87	29 - 67

Variables	N	Percentage
Sex		
Male	107	61%
Female	70	39%
Diagnosis		
Brain tumor	108	61%
ALL	69	39%
Type of treatment		
Surgery only	34	19%
Chemotherapy only	53	30%
Combination	67	38%
BMT	23	13%

Table 3

Demographic and Dependent Variable Summary (N = 177)

Variables	N	Percentage
Age at diagnosis		
> 1 year	8	5%
1 - 3	51	29%
3 - 6	65	37%
6 - 12	53	30%

Table 4

Counts and Percentages of Categorical NEPSY Composite Scores

<i>NEPSY</i> scores	At expected level	Slightly below expected level	Below expected level	Well below expected level
Attention	86 (49%)	39 (22%)	23 (13%)	29 (16%)
Language	81 (46%)	20 (11%)	44 (25%)	32 (18%)
Sensorimotor	34 (19%)	51 (29%)	58 (33%)	34 (19%)
Visuospatial	101 (57%)	21 (12%)	32 (18%)	23 (13%)
Memory	63 (36%)	36 (20%)	49 (28%)	29 (16%)

Table 5

Intercorrelations Among Variables

Scale	1	2	3	4	5	6	7	8	9
1. Age Diagnosis	-								
2. Diagnosis	.35**	-							
3. Treatment	.03	-.13	-						
4. Attention	.15*	.06	.18**	-					
5. Language	.17*	.03	.25**	.57**	-				
6. Sensorimotor	-.20*	.13	.05	.26**	.37**	-			
7. Visuospatial	-.21**	-.13*	.15*	.28**	.44**	.45**	-		
8. Memory	.02	.14*	.10	.34**	.43**	.27**	.40**	-	
9. BSI	-.03	-.17*	.23**	.16*	.10	-.03	-.07	.02	-

Note. * $p < .05$. ** $p < .01$.

Table 6

Univariate Analysis of Variance for Neuropsychology Factors

Source	<i>Df</i>	<i>SS</i>	<i>MS</i>	<i>F</i>	<i>P</i>
Attention	3	865.45	288.48	6.62	.00**
Language	3	383.77	127.92	2.93	.04
Sensorimotor	3	128.85	42.95	.99	.40
Visuospatial	3	383.77	70.36	1.61	.19
Memory	3	211.07	27.97	.64	.59
Error	105	4680.95	41.79		
Total	177	403102.00			

Note. * $p < .05$; ** $p < .01$

Table 7

Summary of Hierarchical Regression Analysis for Variables Predicting Overall Behavior Problems (N = 188)

Variable	β	t	p
Step 1			
Age at Diagnosis	.01	.13	.89
Diagnosis	-.14	-1.83	.07
Treatment	.21	2.87	.00*
Step 2			
Age at Diagnosis	-.06	-.72	.47
Diagnosis	-.17	-2.03	.04*
Treatment	.20	2.59	.01**
Attention	.17	1.89	.06
Language	.05	.51	.61
Sensorimotor	-.01	-.07	.95
Visuospatial	-.22	-2.35	.02*
Memory	.04	.43	.67

Note. $R^2 = .07$ for Step 1; $R^2 = .12$ for Step 2 ($p < .01$)

* $p < .05$; ** $p < .01$

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